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Editorial

PLACEBO EFFECT, SOCIAL MILIEU, AND THE EVALUATION OF PSYCHIATRIC THERAPIES

TRADITIONALLY, psychiatric therapies have been tried out and continued or discarded largely on the basis of intuitive clinical judgment and without the benefit of controlled research. In recent years, with the increasing interest in research and the rapidly growing array of pharmaceutical and other therapeutic agents, the demand for systematic evaluation of the various therapies has grown. Controlled research can, to be sure, never entirely supersede exploratory work in which clinical perceptiveness and imaginative inference are more important than rigorous design. Nevertheless, it has become clear that numerous controls must be utilized in the total evaluation of any treatment. In this paper we are concerned primarily with the evaluation of drugs, but the principles we consider are the same for any form of therapy.

It is not enough merely to administer a therapy and then assess the nature and extent of change in the patients treated. Of the many hazards in this procedure, perhaps the greatest is the placebo effect. The patient may show definite improvement following treatment even when the drug is a placebo, i.e., when it has no specific, disease-combatting efficacy. Symptomatic improvement may be induced psychogenically if the patient attributes healing powers, perhaps in a "magical" way, to the drug, the therapist, or the institutional setting. As Shapiro[1] has shown, deliberate or unwitting reliance on the placebo effect is part of the fabric of medical history. And, as he has also demonstrated,[2] the placebo effect in psychiatry was given relatively little thought or study until very recently.

In attempting to control for a possible placebo effect, investigators have come to rely heavily upon the "double blind" research design. In this design, half the patient sample is given the therapeutic agent being evaluated while the other half is given a placebo which is, ideally, identical to the agent in appearance and immediate perceived effects. Both the patients and the staff are "blind"

as to which patient is receiving which product. The average amount of change in the "treatment" group can then be compared to the corresponding change in the "placebo" group. The effectiveness of the therapy is indicated not by the absolute amount of change it induces, but by the differential gain beyond that brought about by the placebo.

There is an important difficulty in the double blind procedure; the participants in the research may not be truly "blind." Different investigators, observers, ward personnel, and patients may differ greatly in their expectations and discriminations. Some personnel and patients are highly skilled in distinguishing drug from placebo; others are unable to differentiate. This problem has only recently been given the attention it deserves, in studies by Myers, Lasagna, Pfeiffer, and others. A recent double blind study on Marsilid[3] showed that observers' assessment of patient improvement varied directly with their success in judging which patients were receiving the drug. The observers who were most successful (beyond a chance level) in predicting which patients had received Marsilid were also the ones who evaluated the tranquilized patients as most improved. Correspondingly, the observers who predicted least well were the ones whose ratings of improvement showed no difference between drug and placebo groups. This is not to say, of course, that the more perceptive observers engage in deliberate, conscious distortion. It is, perhaps, an example of the influence of knowledge (and wish) upon judgment. Again, Feldman[4] has shown that psychiatrists' evaluation of their patients' response to chlorpromazine were related to their prior attitudes toward the drug. Clearly, it is important to take into account the often subtle values, preferences, and perceptivenesses of the research staff and subjects.

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There is, however, a more fundamental criticism of a theoretic nature. This criticism concerns the rationale or paradigm usually given for the double blind design. The usual paradigm is a simple one. Let R_t and R_p refer to the response to therapy and to placebo, respectively. And let E_t refer to the effectiveness of the therapy. Then it is assumed that: $R_t - R_p$ is determined solely by E_t. In many studies, no other factors are taken into consideration.

Various lines of evidence suggest that this view is narrow and oversimplified. The R_t and R_p and the size of the difference between them depend not merely upon the potency of the therapeutic agent but also upon various features of the psychosocial environment within which the research is carried out. The gross effect of a drug does not depend alone upon its specific somatic impact. Rather, the gross effect depends upon the patient's psychologic state (response set) which in turn is influenced by the character of the environment. In one environment we may obtain a placebo response of +5 and a drug response of +50, while similar patients in a very different environment may show a placebo response of +10 and a drug response of +75. Moreover, the differential response between placebo and drug may be linear or nonlinear depending upon the operation of unknown and uncontrolled variables.

In other words, the double blind procedure tells us how effective a given drug is (as compared with placebo) *under particular psychosocial conditions*, e.g., therapeutic orientation of staff, emotional atmosphere of ward, and the like.

Adequate evaluation of a drug requires that it be tested under a variety of conditions and that these be specified in the design and analysis of the research.

The very process of carrying out research on treatment often leads to a mobilization of the therapeutic resources (psychologic, social, and physical) of the hospital setting. That is to say, the research may produce changes in the milieu—changes which are beneficial in themselves and which increase the patients' responsiveness to specific therapies. Although there is little in the way of rigorous data along these lines, we have some evidence to suggest that therapeutic use of the social environment may be at least as helpful as many of the drugs and somatic therapies now in use. We shall consider briefly some of these observations and their implications for treatment evaluation.

THE THERAPEUTIC RELEVANCE OF THE SOCIAL MILIEU

Persons of experience in mental hospital work have long known of the remarkable influence of physical and social environment, staff morale, and therapeutic atmosphere upon patients' behavior and recovery. However, systematic study of the social environment of the mental hospital is a very recent development. Within the last decade, social scientists and psychiatrists have started to join forces to achieve a better understanding of the formal and informal organization of the hospital, and to manipulate these with the aim of improving patient care. Efforts to analyze the hospital social system and its effects have been made by Jones,[5] Stanton and Schwartz,[6] Greenblatt, York, and Brown,[7] Greenblatt, Levinson, and Williams,[8] Cumming,[9] and Caudill.[10]

In our own experience at the Massachusetts Mental Health Center (Boston Psychopathic Hospital), it was almost entirely social changes that were effective in reducing radically disturbed untoward behavior and the use of continuous baths, chemical restraints, forced feedings, wet sheet packs, and seclusion. Data on the reduction of continuous bath treatments during the period 1925 to 1946 are given in Table I.

TABLE I. DECREASING USE OF CONTINUOUS BATH TREATMENTS
(Boston Psychopathic Hospital, 1925 to 1946)

YEAR	PATIENTS RECEIVING BATH TREATMENT	NUMBER OF BATH TREATMENTS	AGGREGATE BATH HOURS	HOURS PER TREATMENT
1925	730	3,569	24,920	7.0
1930	462	2,422	15,374	6.3
1935	548	2,141	13,841	6.5
1940	318	1,466	7,704	5.3
1941	341	1,419	8,101	5.7
1942	335	1,482	8,412	5.7
1943	*	721	4,317	6.0
1944	178	1,105	5,594	5.1
1945	103	605	3,257	5.4
1946	2	4	8	2.0

*Not available.

In 1925, 730 patients received 3,569 bath treatments for an aggregate soaking of 24,920 hours and an average treatment period of 7 hours. There was progressive decrease until virtual elimination of the bath treatments was accomplished in 1946 and finally the baths were removed altogether. During the period the bath treatments were thought necessary, patients were highly disturbed and agitated on these wards. While some may have profited from continuous baths, others doubtless suffered from the prolonged limitation of movement, and patient care as a whole tended to suffer. A close personal relationship was discouraged by this procedure, for it was felt that the bath alone would accomplish some special good. The elimination of baths and of chemical restraints, forced feedings, and so on was made possible by emphasis upon interpersonal relations and upon uncovering the motives behind excited behavior, which so often leads to punitive restrictive measures.

The story on seclusion is similar as can be seen in Table II.

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TABLE II. DECREASING USE OF SECLUSION
(All Wards of Boston Psychopathic Hospital, January, 1947 to January, 1949)

	PATIENTS IN SECLUSION	PATIENT-HOURS IN SECLUSION	HOURS IN SECLUSION PER PATIENT
January, 1947	28	673	24.0
January, 1948	22	405	18.4
January, 1949	10	46	4.6

Only when seclusion was attacked as a problem resulting from poor social relationships on the ward was it possible to reduce radically the hours, number of patients, and average time in seclusion. In the 9 years since the effective low point reached in 1949, there has been little change in the seclusion rate. Here, again, we found that seclusion was largely a function of tensions, angers, and protests registered by the patient in the form of unacceptable or intolerable behavior. Careful consideration of the emotional meaning of current relationships in the ward setting plus gradual enlightenment and instruction of the attendants and nurses paved the way for diminished use of seclusion. In his monograph, *Experiencing the Patient's Day*, Hyde[11] spells out the kind of education of attendants so necessary to make possible better relationships with patients and virtual elimination of seclusion, baths, restraints, and other impersonal therapeutic measures.

Similar experiences in the reduction of untoward behavior, seclusion, removal of tubs, and the like have been reported by many other centers. Through social manipulation dramatic changes in patient behavior and in ward atmosphere have been produced—from reduced breakage of furniture to improved behavior at meal time, less isolation, more interest in the group, and greater willingness to undertake occupational and work activities. Frequently, along with these changes, there are reductions in overt symptoms and in psychotic process.

For many years men and women had been kept totally apart in this hospital. This policy reflected a specific pattern of fears and resistances, primarily anxiety

over sexual wishes and fear of criticism from relatives and public authorities should any indiscretion occur. However, we observed a marked improvement in our patients when for the first time men and women were permitted to mingle together in occupational and recreational activities. Men responded by tucking in their shirttails, buttoning their trousers, combing their hair, and using more appropriate language. Women took increased pride in their personal appearance. Men and women developed friendships which added meaning and interest to their lives. Aggressive or crude sexual behavior diminished sharply as sexual interest was directed into mutually satisfying forms of socialization. Although for a long time it was considered foolhardy, even dangerous, to bring men and women patients together, the actual events showed how unduly pessimistic were the predictions and how much patients could be trusted.

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The results of a socializing experiment[7] carried out at the Metropolitan State Hospital on a chronic women's ward are of interest here. They were achieved almost solely through the efforts and creative imagination of students and affiliating nurses. Ten or 12 students participated in this "special therapy program." Of the 74 chronic patients, 80 per cent had been diagnosed as schizophrenic, more than half were over 50 years of age, and the vast majority had been hospitalized for 5 years or longer. Among them were disturbed and incontinent patients, fixed chair-sitters, aimless pacers, and incoherent talkers. Many were without shoes and stockings. Not more than 2 to 4 students were available at any one time for activity therapy on this ward. There were weekly meetings with a nursing supervisor. In addition, the students were asked to assess the level of social interaction on the ward by means of a simple scale developed by Wells and Gilbert.[12]

Space does not permit a detailed discussion of the log. Suffice it to say that the student nurses introduced reading material, games, and puzzles; they organized the patients into recreational groups and undertook a program of improving their dress and personal appearance; they managed to take the more interested patients to off-the-ward activities and added music and color to the ward scene. In the first week of May, 1952, before definitive social therapeutic steps were taken, 4.1 per cent of the patients were engaged in constructive activity (as measured by the rating scale) on the ward. By May, 1953, 39.4 per cent of patients were engaged in constructive activity on the ward when the students were around to help them, and without students' presence, 22.3 per cent. Isolated activity as well as aggressive and abusive behavior diminished markedly. Patients assumed a larger responsibility for themselves and the ward atmosphere changed altogether.

It is of particular interest that when the student program ended, the ward lost its enthusiasm and patient behavior slumped to its former level. We do not know what level of improvement the ward might have achieved had the experiment continued for a longer time. Clearly, social therapeutic changes do not occur unless energy, enthusiasm, and interest are brought into the social system. If a drug had been given during this period, equal gains might have accrued, but how much would have been due to drugs alone?

A similar point of view is expressed in the report of the Expert Committee on Mental Health of the World Health Organization.[13]

> The most important single factor in the efficacy of the treatment given in a mental hospital appears to the committee to be an intangible element which can only be described as its atmosphere. . . . As in the community at large, one of the characteristic aspects of the psychiatric hospital is the type of relationship between people that are to be found within it. The nature of the relationships between the medical director and his staff will be reflected in the relationship between the psychiatric staff and the nurses, and finally in the relationship not only between the nurses and the patients, but between the patients themselves.

IMPLICATIONS FOR RESEARCH

The social context of hospital and ward is, it would seem, a powerful force influencing the results of any clinical research that produces change in the amount and modes of patient interaction. The psychosocial environment ordinarily has mixed, pro- as well as contratherapeutic, consequences. It is unrealistic and theoretically limited to conceive of the environment merely as a "source of experimental error," as something to be eliminated or cancelled out in order to assess the "true" effectiveness of the therapy per se. The potential of any agent is influenced by the social conditions under which it is administered. It is therefore not surprising that evaluation studies in different settings often yield widely differing results. An adequate evaluation of any therapy can emerge only from consideration of its effects under various circumstances. To take but one example, it has often been observed that a drug or other therapy is found to be more effective during a period of great therapeutic interest and zeal than during a later period when its application has become more routinized. Perhaps we need to take into account not only the immediate treatment milieu but also the historical scene within which the experimental drama of a double blind study is enacted.

In the long run, then, evaluation research must be viewed in sociopsychologic as well as somatic and other perspectives. Greater attention will have to be given to specifying environmental variables that mediate response to specific therapeutic procedures. While research along these lines is still in its infancy, studies such as those mentioned earlier have made some progress in identifying and measuring important variables. For example, we can ascertain the relative emphasis on custodial as against therapeutic functions in hospital structure and in staff ideology.[8] One might suppose that a drug will produce greater effects in an actively therapeutic setting than in one concerned primarily with security measures and custodial care. A case might equally be made for the opposite hypothesis: that a drug will have its strongest effect in a custodial environment where social stimulation and interaction are minimal and the ceiling for improvement is high. A corollary prediction is that in a psychologically rich environment the drug can add little since a large measure of the patients' capacity for improvement has already been activated by other means. More complex formulations will no doubt be needed as our theory, techniques, and findings develop in this area.

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Numerous other types of variables are being subjected to investigation: ward climate and interaction patterns, staff morale, staff values and assumptions concerning the kinds of patients who deserve particular treatments or who are likely to benefit therefrom, institutionally patterned ways of humiliating patients or of strengthening their sense of personal dignity and self-determination, and many others. The subtle forms of relationship within the hospital, the prevailing images of patient, nurse, and doctor, and many other aspects of hospital life must eventually be grasped, conceptualized, and at least crudely measured. If we continue to ignore these tasks, we lose on many fronts: we do poor research on treatment evaluation; we narrow our treatment horizons; and we close our eyes to a valuable opportunity for the development of biopsychosocial theory and research.

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STUDIES ON THE OCCURRENCE OF BACTEREMIA IN RHEUMATIC FEVER

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WE have found, during the course of our studies, an unusual number of positive blood cultures in children with rheumatic fever. The organisms obtained in these cultures are short-chained gram-positive streptococci and are often diplococcal in form. They have been identified by both biologic and serologic methods, and appear to be similar to the nonhemolytic streptococci which were described a number of years ago by earlier workers. A matched group of control cultures have not revealed this organism.

The Group A, beta hemolytic streptococcus, has unquestionably been shown to be etiologically related to rheumatic fever. There are, however, many unanswered questions in regard to the persistence and the chronicity of this disease in many of its victims. Rheumatic fever occurs in a relatively small and somehow selected number of those patients who develop a Group A streptococcal infection. This report is being submitted in the interest of raising the possibility of an additional or related factor in the pathogenesis of this disease.

REVIEW OF THE LITERATURE

The question of bacteremia in rheumatic fever has been a recurring problem for more than half a century. The concept which is currently dominant holds that no organisms are culturable from the blood or the tissues in this disease.

A cooperative study by the Hektoen Institute for Medical Research of the Cook County Hospital; the University of Illinois College of Medicine; the Cook County Children's Heart Station; and the Chicago Medical School.

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This belief, however, is founded upon work that has not been repeated for more than twenty-five years. It is difficult, after this span of time to explain the almost universal acceptance of the finding of negative blood cultures in rheumatic fever.

We felt it important, therefore, to present in considerable detail a review of the older literature since there is no body of current work or writing with which to compare our findings. The review is divided into two parts: first, studies on postmortem blood and tissue cultures in patients who had died of rheumatic fever; and, second, studies which attempted to obtain blood cultures from the living patient with this disease.

POSTMORTEM STUDIES

The finding of streptococci in pathologic specimens was described by Dana[1] in 1894. He found microscopic evidence of diplococci in the brain in a patient with chorea 24 hours after death, and he was able to culture these organisms. Westphal, Wasserman, and Malkoff[2] in 1899 also found a diplococcus in the blood postmortem and cultured this organism from the heart valves of a young girl who died during an attack of chorea. Reye[3] in 1903 felt that he could always demonstrate diplococcal organisms in rheumatic endocarditis microscopically. The heart blood was sterile at postmortem, but, upon scratching the surface of the valve and culturing this material, he was able to culture a diplococcus in 8 out of the 23 cases in which the streptococcus had been visible. In 1919, however, Epstein and Kugel[4] emphasized that agonal cultures and necropsy specimen cultures may not be valid since a large number of all types of patients showed greater than 50 per cent positive cultures. Eighty-six per cent of their organisms appeared to be enterococci, and this seemed to disprove any degree of specificity for this streptococcus in relationship to rheumatic fever.

The question was reopened by Green[5] in 1939, who investigated the specimens from 9 patients with rheumatic fever and 22 control patients. He found that 8 of the cases that showed microscopic rheumatic lesions showed streptococci in the valves and that only 2 in the larger control group showed such organisms. Mallory and Keefer[6] in 1941 also found streptococci in the Aschoff nodules in cases of early fatal rheumatic fever. Collis[55] was able to culture the streptococcus in 22 of 42 heart valves despite the fact that 12 blood specimens from the heart taken at the same time were negative on culture. The question of postmortem cultures then seems still to be an open one, but it would appear to be exceedingly difficult to rely on the finding of streptococci on the valves or in the heart in view of the work of Epstein and Kugel.

BLOOD CULTURES

The second portion of our review, that of blood cultures taken during life in patients with rheumatic fever, constitutes the basis for a large body of literature since 1887. The bacillus of Achalme appeared early, and numerous investigators were able to demonstrate this large bacillus, but this was gradually superseded by the streptococcus or diplococcus of other workers. More recently

Callow[53] and others have felt that the two forms, one bacillary and the other coccal, may bear some relationship to each other.

Mantle[7] in 1887 found 100 per cent of blood cultures positive in 16 cases of acute and 10 cases of chronic rheumatic fever. In 1896 Leyden[8] described 5 positive cultures for the diplostreptococcus in acute rheumatic fever. Triboulet and Coyon[9] found positive cultures in 5 and 11 consecutive cases of rheumatic fever. In some the diplococcus was visible in large numbers by direct examination of the blood, and in others only a few were seen.

Poynton and Paine[10] in 1900 found a diplococcus in the blood of 8 patients with rheumatic fever while searching for Achalme's bacillus. The description of the organism and its biochemical characteristics were those of the present-day enterococcus group. They reproduced what they felt was rheumatic fever in rabbits and named the organism the *Diplococcus rheumaticus*. Beaton and Walker[11] in 1903 cultured 15 similar organisms from rheumatic fever patients; 4 from the blood, 1 from the joint, 3 from the urine during life, and 7 from post-mortem blood. Ainley Walker[12] in 1903 made the statement, in a review, that the diplostreptococcus had been proved to be the cause of rheumatic fever. Lewis and Longcope in 1904[13] cultured from the blood of a patient with rheumatic fever 12 hours before death the same diplococcus as had others, and developed with it a nonsuppurative arthritis in rabbits. McRae,[14] however, in a chart review of 294 patients with rheumatism, out of a total admission of 14,567 cases, stated in regard to blood cultures taken at The Johns Hopkins Hospital, "it is disappointing to report that our results throughout were practically negative, cultures from the joints, the blood, and the urine yielding nothing positive." Rufus Cole[15] in 1904 also used 7 strains of streptococci from various sources including one from rheumatic fever to induce arthritis in rabbits. He found no difference in the arthritis caused by the so-called rheumatic strain and felt therefore that it was not a specific organism. C. Phillip[16] in 1903 found, by what appeared to be extremely careful technique, in 21 cases by blood culture, and in 6 cases by joint fluid culture under prolonged incubation, not one positive culture.

Beattie[17] felt that the arthritis produced in rabbits by the rheumatic coccus was definitely different and nonsuppurative in comparison with the suppurative arthritis produced by the hemolytic streptococcus. Charlton[18] confirmed Beattie's work and found a micrococcus from the blood in 3 cases of rheumatism which produced arthritis without pyemia in rabbits. Loeb[19] in 1908 isolated a diplostreptococcus in 11 of 45 cases from the blood and joint fluids in rheumatic fever, but he concluded that the streptococcus isolated was unlikely to be the causal agent as it failed to show any features which differentiated it from other members of this group. Camisa[20] in 1910 found diplostreptococci in 6 cases of 9 with chorea; Beattie and Yates[21] in 1912 found 3 of 11 blood cultures from rheumatic patients positive. They felt that the terminal infection or agonal false positives were definitely ruled out by their technique.

Harrison[22] in 1913 cultured blood from 26 cases of rheumatic fever with no bacterial growth except in one which was considered a case of endocarditis lenta. As a general statement in 1915 Koplik[23] said, "I have diligently cultured the blood in many cases of chorea, but have failed to find any micro-organisms."

Herry[24] in 1914 gave a fresh start to the streptococcus studies. He cultured the blood from 60 cases of rheumatic fever in young adults using 6 to 8 tubes for each specimen; if one tube was positive, all were positive. In 46, or 78 per cent, of his cases, he found a diplostreptococcus resembling that of Poynton and Paine. Morse and Floyd[25] 2 years later found only 4 positive cultures in 26 cases of chorea. Moon and Edwards[26] in 1917 studied rheumatism with or without carditis and found in acute arthritis 13 positive cultures for a nonhemolytic streptococcus out of a total of 40 cases, and in chronic arthritis (probably rheumatoid) 18 nonhemolytic streptococcal cultures out of 83 cases. No controls were used in this study, however. Swift and Kinsella[27] found only 8.3 per cent positive cultures in 85 samples taken from patients with rheumatic fever. W. Lintz[28] in 1918 found 4 positive cultures of nonhemolytic streptococci from the blood of patients with rheumatic fever. He made the interesting observation that these organisms remained viable after drying for as long as 6 and 11 months. It was also his feeling that the organisms were trapped in the Aschoff body and therefore not easily culturable from the blood. In 1918 Quigley[29] studied the bacteriology of chorea, taking only the cases with no heart involvement. In 21 cases in which blood cultures were taken he found 10 positive for a diplostreptococcus. In 21 cases of spinal fluid from such patients, there were 13 positive cultures for this organism. He maintained his cultures for 4 weeks instead of the usual 14 days. Richards[30] in 1920 took blood cultures in 104 cases of arthritis and chorea. He found 20 positives, the organism usually being a viridans streptococcus. In a comparable control series he found no such organisms. He added the observation that the organism did not grow out secondarily on plates with a high content of blood and wondered whether "it may be that whole blood itself acts to inhibit the development of growth." Freund and Berger[31] also performed a large and well-controlled survey of blood cultures in 1924. They found that, in 23 cases of rheumatic fever, there were 15 positive cultures containing a "Greening" streptococcus. This ratio was almost as high as that of positive cultures which they obtained in endocarditis lenta and acute endocarditis or sepsis, but no follow-up study was apparently done by these workers.

In 1924, also from a somewhat different approach, there was further indirect evidence of positive cultures in rheumatic fever. Capps[32] described 57 cases of subacute bacterial endocarditis in patients alive after 2 years. It appears likely in that preantibiotic era that many of these were actually cases of rheumatic fever in which a positive culture had been obtained. The diagnosis of endocarditis lenta was a bacteriologic one. Graham, Oille, and Detweiler[33] in their report to the American Association of Physicians in 1924 discussed their series of 23 cases of *Streptococcus viridans* bacteremia 9 years after diagnosis, in 22 of which mitral systolic murmurs had developed, in 9 aortic diastolic murmurs, in 3 mitral presystolic, and in one no murmur. At least some of these were, in all likelihood, cases of rheumatic endocarditis rather than of subacute bacterial endocarditis. Miller at the same meeting also described his follow-up of 8 patients who had had positive blood cultures. Four of these had the clinical symptoms of subacute bacterial endocarditis and died. Four had the symptoms of rheumatic fever and were still alive. In all these examples, while it is not

specifically so stated, it is very likely that the diagnosis in the patients who survived was actually rheumatic fever.

Clawson[34] in 1925 used the clotted blood culture technique. He had originally found a lens-shaped diplococcus in the blood of a mother with rheumatic fever and in the joint fluid of her newborn infant. He went on to isolate the same organism in 20 cases, 13 of them from the blood of patients with rheumatic fever before death, 2 from the joint fluid, and 5 from necropsy specimens. He felt the organism to be an enterococcus. Small[35] 2 years later isolated a streptococcus with what he felt was a specific immunologic identity from the blood of a patient with rheumatic fever. He named the organism the *Streptococcus cardioarthriditis*. Birkhaug[36] in 1927 did a similar piece of work on the basis of only one organism isolated from a 5-year-old girl's blood during life, and postmortem from the heart valves. He did very careful biochemical studies with this microorganism and was convinced that a toxic filtrate was responsible for the disease. Skin tests with this organism were positive in patients with rheumatic fever, and he went so far as to inject the bacterial filtrate into himself and developed a "typical" picture of rheumatic fever with arthritis.

The last two workers, while doing very thorough biochemical and immunologic studies, based their conclusions on only two organisms that were cultured and no controls were employed. Many authors soon found organisms of the Birkhaug or Small type in normal throat cultures. Lynch[37] in Canada stated that his attempts to culture a bacterium in acute rheumatic fever by the clot technique were unsuccessful. His series, however, was small—only 20 cultures from 15 patients, of which 2 were discarded by accident and 13 were contaminated by *B. subtilis*, Proteus, *Staph. albus* or molds. As he stated, on the basis of this work, the refutation of Clawson's work was neither "justified nor implied."

Irvine-Jones[38] in 1928 performed blood cultures according to the technique of Clawson, but was unable to culture the streptococcus from 33 blood cultures taken from 29 patients; only contaminants were found. Suranyi and Forro[39] had apparently better results in the same year. In a controlled series of cases they found 68 per cent of 25 cases of polyarthritis positive for anhemolytic streptococci. They also found, however, a high percentage of positive cultures in cases of pernicious anemia with fever. Lazarus-Barlow[40] the following year cultured 33 cases by Clawson's technique; he found no positives and five contaminants. Cecil, Nicholls, and Stainsby[41] in 1928 awakened the waning interest in the bacteriology of rheumatic fever with their study of 29 blood cultures from rheumatic patients. They found viridans streptococci in 9 cases, a percentage of 31 per cent positive. In 1929, using what they felt to be a more careful technique, they cultured the blood of 31 more rheumatic patients and found 26 cultures positive, a percentage of 83.9 per cent. A series of 66 control cultures was run on nonrheumatic patients and only one positive streptococcal culture was found. They indicated the importance of prolonged incubation. In one instance no growth occurred until 6 weeks of incubation had elapsed. They also mentioned the difficulty of obtaining growth on the first subculture.

This latter work seemed quite clear-cut, and yet the following year Dawson, Olmstead, and Boots[42] contradicted Cecil's work on rheumatoid arthritis. They

took 105 cultures on 80 patients, and 31 controls from 16 patients, and 16 tubes of sterile agar manipulated by the technique of Cecil and Stainsby. Their results were so poor that they were prompted to conclude "that the technique is so involved as to call into question the significance of all bacterial growth encountered."

Others took up the work but did little to dispel the discrepancies, since the results were rather equally divided into positive and negative reports. Nye and Waxelbaum[43] in 1930 stated that they were unable to confirm Cecil's work despite the fact that they obtained growth of a nonhemolytic streptococcus in 5 of 7 patients with rheumatic fever from whom blood cultures had been taken. They used several tubes and flasks for each patient, and because growth did not occur in all tubes and flasks, the growth which did occur was not considered significant. Gibson and Thomson[44] found 6 blood cultures negative in 1929. Nye and Seegal[45] in 1929 cultured blood from 25 cases of acute rheumatic fever. They found not one positive culture, but only contaminants. Their first subculture was made to blood agar plates.

Bernhardt and Hench[46] in 1931 questioned Cecil's work on patients with rheumatoid arthritis, finding no positives in comparison with Cecil's 70 per cent in these cases. Jordan and Boland,[47] however, in 1930 found in 21 patients whose blood did not show contamination on culture, 12 positive for short-chain streptococci. In 17 uncontaminated control cultures there were no such organisms. Gray and Gowen[48] in 1931 duplicated Cecil's work on rheumatoid arthritis, finding 46 positive cultures in 71 cases of rheumatoid arthritis, and 5 positives in 13 cases of acute rheumatic fever.

Attempting to determine the validity of the results in those with a high contamination ratio, Cameron, Rae, and Murphy[49] took 100 cultures from the blood of unselected patients; 20 c.c. samples were taken and incubated for one month. They found only 6 positives, 4 being *Staph. aureus* and 2 diphtheroids. No streptococci were found. This work is at great variance with that of Dawson and Nye previously described, and with that of May Wilson[50] who reported in 1933 that of 536 blood cultures drawn on varying types of patients, 147 were contaminated. Twenty-five per cent of the remaining or uncontaminated group of 389 cultures showed growth of what was described as pleomorphic bacilli. Forty-six per cent of the cultures from 236 rheumatic patients were positive, and 41 per cent of 153 control cultures were positive. Included were those from patients with subacute bacterial endocarditis, pneumonia, and respiratory disease, and from 10-day-old infants. The conclusion of the author was that, since the ratio between the controls and the rheumatic patients was so nearly equal, the cultures were of no significance. Cooley[51] in 1932 at the Cook County Hospital cultured the blood of 25 children with rheumatic fever and 10 control patients, 6 and 2, respectively, being contaminated with molds. He did not obtain streptococci or bacilli from either patients or controls.

Lichtman and Gross[52] in 1932 reviewed a series of 5,233 hospital blood cultures. Of this group 188 were called rheumatic fever. This group had 20 positives. One-hundred fifty-eight of these were routine blood cultures and 30 were taken by the special methods such as those described by Cecil. Their percentage

was 8 per cent in acute rheumatic fever and 6 per cent in controls. This work is difficult to interpret since subacute bacterial endocarditis was not included in either group and, since only 23 of the 144 cases diagnosed as subacute bacterial endocarditis came to postmortem, one cannot determine whether a considerable number of cases of rheumatism were not ruled out of consideration on the bacteriologic diagnosis of subacute bacterial endocarditis. Callow[53] in 1933 presented a large series of blood cultures in patients with rheumatic fever. The organisms obtained appeared to show dissociation between an anhemolytic or viridans streptococcus and a pleomorphic bacillus. She considered them together in reporting the number of positives. Of the 174 patients from whom these cultures were taken, 122 or 70 per cent had one or more positive cultures. The same organism was cultured from 66 per cent of a group of patients with tonsillitis and measles. Other controls with varying febrile and nonfebrile illnesses showed 30 per cent positives. In her series only 8 per cent of normal persons showed any organisms on blood culture. The streptococci were classified as *Str. faecalis*. The pleomorphic bacilli changed to the diplostreptococcus repeatedly, but the reverse did not appear to occur. Howell and Burton[54] in 1934 were un-

TABLE I. BLOOD CULTURES POSITIVE FOR DIPLOSTREPTOCOCCUS IN PATIENTS WITH RHEUMATIC FEVER CONSIDERED OF SIGNIFICANCE* BY AUTHORS

YEAR	AUTHOR	PATIENTS	POSITIVE	
			NUMBER	PER CENT
1887	Mantle	26	26	100
1896	Leyden	5	5	100
1897	Triboulet and Coyon	16	16	100
1900	Poynton and Paine	6	6	100
1903	Beaton and Walker	4	4	100
1904	Lewis and Longcope	1	1	100
1906	Charlton	3	3	100
1910	Camisa	9	6	66
1912	Beattie and Yates	11	3	33
1914	Herry	60	46	78
1917	Moon and Edwards	40	13	33
1918	Quigley	21	10	50
1920	Richards	104	20	20
1924	Freund and Berger	23	15	65
1925	Clawson	20	13	65
1928	Suranyi and Forro	60	44	73
1928	Cecil, Nicholls, and Stainsby	29	9	30
1929	Cecil, Nicholls, and Stainsby	31	26	83
1930	Jordan and Boland	21	12	57
1931	Gray and Gowen	13	5	38
1933	Callow	174	122	70
	Total	677	405	60

*"Significance" here denotes the separation of the various authors into two groups: first, into those who did and, second, those who did not believe that the streptococci found by themselves or others were related to the rheumatic disease in the patients studied. The group with the negative viewpoint were inclined to feel that those positives which they may have found were either contaminants or would be found in all patients whether or not rheumatic fever was present.

successful in producing this type of dissociation. They did, however, recover 4 streptococci from patients with acute rheumatic fever; 2 were nonhemolytic, 1 hemolytic, and 1 viridans.

Collis[55] in 1939 reviewed the bacteriology of rheumatic fever and stated that in 144 cases from which he had cultured blood, no positives were obtained.

Despite, then, this rather extensive review of the bacteriology of the blood in acute rheumatic fever, the question appears to be a still unsettled one after more than 50 years of attempt at clarification.

Since we found, however, a rather high percentage of positive streptococcal cultures in our patients with acute rheumatic fever, a repeated examination of the literature was directed at an attempt to separate the factor of culture alone from the factors of interpretation and specific identification of the organism by the authors. No credence or consideration was given to the naming of a specific organism such as the *Streptococcus cardioarthriditis* or the *Diplococcus rheumaticus;* nor whether any attempt was made to reproduce the rheumatic state in animals. It was found early in this review that the criticisms leveled at the previous studies were generally not directed at the fact that the organism was found in the blood

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TABLE II. BLOOD CULTURES IN RHEUMATIC FEVER CONSIDERED OF NO SIGNIFICANCE* BY AUTHOR

YEAR	AUTHOR	PATIENTS	POSITIVE	
			NUMBER	PER CENT
1904	Cole	1	1	100
1903	Phillip	21	0	0
1908	Loeb	45	11	24
1913	Harrison	26	1	4
1916	Morse and Floyd	26	4	15
1917	Swift and Kinsella	85	7	8.3
1927	Lynch	15	0	0
1928	Irvine-Jones	29	0	0
1929	Lazarus-Barlow	33	0	0
1930	Nye and Waxelbaum	7	5	71
1929	Gibson and Thomson	6	0	0
1929	Nye and Seegal	25	0	0
1933	Wilson and Edmond	67	31	46
1932	Cooley	25	0	0
1939	Collis	144	0	0
	Total	555	60	10.8
	Chart Reviews			
1903	McRae	294	0	
1932	Lichtman and Gross	188	20	
	Total	482	20	4.8

*"Significance" here denotes the separation of the various authors into two groups: first, into those who did and, second, those who did not believe that the streptococci found by themselves or others were related to the rheumatic disease in the patients studied. The group with the negative viewpoint were inclined to feel that those positives which they may have found were either contaminants or would be found in all patients whether or not rheumatic fever was present.

culture, but that it was considered to be a specific streptococcus and that it alone was capable of reproducing the rheumatic state in animals. Many other nonhemolytic streptococci were always found to produce the same picture in these animals. The only evaluation which we have made in the following tabulation is the presence or absence of the short-chain streptococcus, and the number positive or negative in each study. This tabulation is presented in Tables I and II.

When we examine these tables it becomes quite apparent that a considerable number of authors holding both the negative and positive views have cultured this type of organism from the blood in cases of acute rheumatic fever. As we examined the techniques and methods it seemed that in most cases when the investigator was sufficiently interested and persistent and used great care and the best culturing methods of the time the yield of positive cultures was quite high. We must add, however, that only a few of these studies were well controlled, and each again in turn could be criticized on the basis of specificity or reproducibility. On the other hand, many of the negative studies were routine chart reviews, personal opinions, or sweeping statements such as, "We have not found by careful technique these positive cultures," without specific statements as to how many were found and what the techniques were.

In view of the still present question of the presence or absence of an anhemolytic streptococcus in the blood of patients with acute rheumatic fever, we felt it worth while to report our results in a controlled study of blood cultures without immediate consideration of their significance in the etiology or pathogenesis of this disease and then to attempt to propose some theoretical relationships with the previously well-documented work upon the Group A streptococcus in rheumatic fever.

PRESENT INVESTIGATION

Interest in this investigation was the result of the clinical observation that a small series of patients with chronic relapsing rheumatic fever did not show an immediately measurable response to high dosages of penicillin given therapeutically. Intravenous pencillin was given in dosages from 10 to 60 million units daily for a period of weeks with no appreciable clinical effect except for an occasional immediate worsening of the clinical picture as previously described by Watson, Rothbard, and Swift,[57] Foster,[58] Gubner and Szucs,[60] and Rantz and associates.[59]

The Group A beta hemolytic streptococcus appears to serve as the inciting agent in the rheumatic process. This seems to have been amply documented by the work of Swift,[62] Coburn,[56] Rammelkamp,[61] and many others. The disease is, however, not an immediate or suppurative complication of the streptococcal infection, but a nonsuppurative response, possibly on the basis of host sensitivity of the tuberculin type. In addition to the clinical evidence, there is a large body of supporting literature on the rise in antibodies to various components and products of the streptococcus which herald and accompany the disease in almost all instances in the work of Todd,[63] Stollerman,[64] Stetson,[65] Harris,[66] and McCarty.[67]

It seemed, then, logical to assume that perhaps the Group A streptococcus occupies the same antigenic relationship to the disease rheumatic fever, as does the tubercle bacillus to the state of tuberculin allergy which is responsible for many of the clinical signs of tuberculosis in its secondary stage. It should then be possible to eliminate the disease by destroying the organism with an antibiotic such as penicillin just as one would in tuberculosis, using streptomycin, if the organism were sensitive to this antibiotic, since pencillin is bactericidal in very low concentration for the Group A beta hemolytic streptococcus.

The fact that this response did not occur was not surprising in view of previous reports, but raised several investigative possibilities:

1. That the Group A beta hemolytic streptococcus had become resistant to penicillin. This, however, has never definitely been shown to occur.

2. That the Group A hemolytic streptococcus is essential only in starting the process and that the disease is a self-perpetuating condition maintained by altered tissue proteins. This would only partially explain the situation in regard to rheumatic fever. A horse serum reaction may manifest itself by repeated attacks of "anaphylactoid" response following a single injection in a sensitive individual, but these occur at close intervals and this reaction then ceases and does not recur unless more serum exposure takes place, while chronic rheumatic fever is a cyclic and recurring disease process.

3. That the highly penicillin-sensitive streptococcus is so well protected and inaccessible to the antibiotic that the factor of insufficient penetrance prevents the eradication of the organism. This degree of host protection for the organism does not easily lend itself to belief since even the highly resistant enterococcus located in the fibrotic heart valves in subacute bacterial endocarditis can usually be killed by a dosage of penicillin such as the one used, over a period of weeks.

4. That the child who is sensitized by the Group A beta hemolytic streptococcus becomes so hyperreactive that the occurrence of fresh Aschoff bodies and the clinical manifestations of rheumatic fever are continued by nonspecific stimuli, either bacterial or others such as trauma, sunburn, or emotional factors. That this may have indeed been the case was suggested some years ago by the work of Massell and Jones[68] and others who showed that reactions to the sulfonamides were much more common during the acute stage of rheumatic fever, and that subcutaneous injections of saline or trypsin could bring about a localized subcutaneous nodule only when given during the acute stage of rheumatic fever, and that these had no such effect between attacks. More recently, however, McCarty[69] and Massell[70] have shown that the rheumatic child during the acute stage is no more capable of reacting to other antigens than is the normal. Antigens such as diphtheria toxin, even when given as a booster dose, had no increased effect in the rheumatic child. The titers obtained were no higher than those obtained in the normal group.

5. That the Group A beta hemolytic streptococcus has the capacity to develop under certain circumstances a highly resistant or "spore" form which, while not culturable by ordinary methods, is still antigenically capable of continuing the disease process begun by the parent organism. This is at least suggested by the work of Dienes,[71,72] Klieneberger,[73] Sharp,[74] and others on the "round

bodies" or pleuropneumonia-like organisms derived by these workers from many bacteria including the streptococcus.

6. Finally, since the separation of the streptococci into various groups and classes is a highly artificial one based only upon their action upon media, the components of their cellular structure, or a portion of their protein content, is it possible that there are just as many similarities between these various streptococci as there are differences? In other words, the invasive capacity of the Group A beta hemolytic streptococcus may enable it to create local tissue sensitivity which may then be maintained by an otherwise almost normally found streptococcic inhabitant of the host, such as the enterococcus. This effect could be due to some as yet undefined antigenic relationship between this streptococcus and the Group A hemolytic streptococcus. This saprophytic type of organism in addition to being highly resistant to penicillin is capable of existing in areas which are not easily accessible to antibiotic agents, such as dental or nasal antral areas, or in any of the crypts of the gastrointestinal tract and the paronychia from which absorption of the bacteria or its components or products is possible. This, too, is certainly suggested by the dramatic effects which sometimes follow the removal of this type of infection in a child with chronic rheumatic fever.

The first five considerations did not seem to be approachable at the present time in our hands, and the last alternative seemed to lend itself most readily to further investigation. It was felt necessary to begin by culturing the throat, blood, abscesses, tooth infections, and any other sites that might appear as a source of infection in the child with rheumatic fever. This report is restricted to the results of the cultures of the blood in patients with rheumatic fever and in a comparable series of nonrheumatic control patients in the same age group.

METHODS

The medium used was a brain-heart infusion containing 0.1 per cent agar. Two ounce square clear glass, screw-cap bottles of the type described by the St. Louis Health Department were used. A rubber diaphragm fitted to the cap allowed needle puncture for introducing the blood sample. Each bottle was charged with 45 c.c. of freshly prepared medium and the screw caps tightened only after autoclaving. A piece of adhesive tape was used to cover the cap prior to sterilization.

Patients were children aged 5 through 15 hospitalized on the wards of the Cook County Hospital and in the Fantus Children's Cardiac Clinic. The diagnosis of rheumatic fever in the patients selected was made upon the basis of the major criteria of Jones supplemented by the confirming laboratory studies of sedimentation rates, antistreptolysin titers and serum mucoprotein levels. The progressive changes in these determinations and the clinical signs of carditis, the electrocardiogram and x-ray examinations were scrupulously applied to document the diagnosis in each case. There was no knowledge of, or reference to, the findings on blood culture in these patients during this evaluation.

The blood was drawn in a small operating room on the children's ward in the hospital or in a similar room in the Fantus Clinic with a member of the team

present on each occasion. The skin was scrubbed for 3 minutes with a throat swab saturated with a solution of nonallergic soap containing hexachlorophene. The excess soap was wiped off with a dry, sterile swab with a widening circular motion and the skin allowed to dry. Five cubic centimeters of blood was withdrawn aseptically and immediately delivered and dispersed into the culture flask. The tape, a corner of which was lifted briefly for the inoculation through the cap memdrane, was replaced and the flask placed in an incubator used only for this purpose. The incubation period was prolonged to from 30 to 35 days. The flasks were opened only when visual turbidity or discoloration developed. Before plating on solid medium a second passage to another tube of brain-heart infusion was frequently necessary despite the fact that the organisms were numerous on direct smear visualization. From this growth, a sample was spread on 5 per cent horse blood agar. Five colonies were picked from this pure culture for further identification. A sample of the identical strains so obtained was maintained and lyophilized.

Fifty of the organisms obtained were studied biochemically and serologically, the details being given elsewhere.[76] The tests used were as follows: heat resistance at 60°C. for 30 minutes; sodium chloride tolerance at 6.5 per cent; bile resistance at 40 per cent; growth at pH 9.6; methylene blue tolerance at 1:1,000; esculin plate; fermentation of mannitol, trehalose, and sorbitol; plate and tube hemolysis using horse blood; penicillin resistance by tube method; and Lancefield precipitin grouping using Group A and D sera which we produced by the method of Slavin,[75] and also antisera obtained commercially from Difco Laboratories against Groups A, B, C, and D.

An age-matched group of 50 children admitted for elective surgery for noninfectious conditions and 50 children with various infectious diseases such as pneumonia, measles, and pharyngitis were selected. Cultures were drawn prior to antibiotic therapy by the same technique as that used in the rheumatic patients.

RESULTS

Usually no growth was obtained during the first 2 weeks of incubation. On continuation of the incubation up to 30 days, however, there was unexpectedly found to be present a short-chained nonhemolytic or slightly beta hemolytic streptococcus often occurring in diplococcal form in the rheumatic cases, as had been previously described by investigators in the past. Feeling that these were probably contaminants, at first no attempt was made to study these organisms other than to describe them morphologically and to determine their action upon horse blood agar plates. After a number of such cultures it became apparent that these organisms were not a fortuitous finding but were frequently cultured in more than one sample from the same patient with rheumatic fever, and were never found in our control cultures taken at the same time. Subsequent cultures were then carefully studied and completely identified.

Table III describes these cultures and their sources. The cases of rheumatic fever are divided into three stages of clinical disease: (1) the acute, representing the first 2 months of the disease from the date of onset of first symptoms; (2) the

convalescent period, representing the time between the second and eighth months following the onset of the first symptoms; and (3) the inactive group, those who have had no symptoms for at least 8 months. The three groups are further subdivided into those who had received penicillin or sulfonamide therapy, in either therapeutic or prophylactic dosage, prior to culture, and those who had received no medication. A small series who had received only salicylate medication are not included because of the limited number, but in 9 such determinations no positive cultures were obtained. It is becoming increasingly difficult in this antibiotic era to obtain patients for study who have not already received medication, usually a repository penicillin.

TABLE III. NUMBER OF CULTURES AND PATIENTS WITH RHEUMATIC FEVER IN THE ACUTE, CONVALESCENT, AND INACTIVE STAGES WITH AND WITHOUT CHEMOTHERAPY OR ANTIBIOTIC THERAPY*

STAGE OF DISEASE AND THERAPY	CULTURES			PATIENTS		
	TOTAL	POSITIVE	PER CENT	TOTAL	POSITIVE	PER CENT
Acute onset to 2 months						
Acute, no therapy	79	41	52	36	24	66
Acute with therapy†	80	9	11	37	9	24
Convalescent 2 to 8 months						
Convalescent, no therapy	13	2	15	9	2	22
Convalescent with therapy	104	9	9	26	6	23
Inactive beyond 8 months						
Inactive, no therapy	58	6	10	53	5	10
Inactive with therapy	51	3	6	24	3	12
Total rheumatic fever	385	70	18	185	49	27
Control						
Febrile controls, no therapy	66	7	11	50	7	14
Nonfebrile controls, no therapy	58	6 (2)	10 (4)	50	6 (2)	12 (4)
Total controls	124	13	10	100	13	13
All Culture Total	509			285		

*This shows number and percentage positive for diplostreptococcus in the rheumatic group and all organisms in the control. Numbers in parentheses in nonfebrile controls indicate the number of diplostreptococci.

†Antibiotics or chemotherapy.

Fig. 1 represents in graphic form the patients who were positive in all groups and controls. It is to be seen from this illustration and Table III that of 79 cultures taken on 36 patients with acute rheumatic fever who had received no medication, 52 per cent and 66 per cent, respectively, were positive and contained a short-chain streptococcus, as compared to 10 to 14 per cent of all types of organisms in the control groups, both febrile and nonfebrile. This difference is actually greater than it appears since in our controls we included

as positive cultures, in addition to the diplostreptococci, 4 cases of definite staphylococcal cultures which all occurred in the samples taken on a single day when no hexachlorophene was available for skin sterilization, and a standard technique was used. Only four contaminants were found in the rheumatic series and were discarded. The chi-square value is approximately 10 times as great as needed to demonstrate a statistically significant difference at the 0.01 level between the acute rheumatic cases and the controls despite the addition of the known contaminants to the control group.

As a further consideration of the figures obtained, it is apparent that the child with inactive rheumatic fever, with no evidence of illness for at least 8 months, actually serves as a control for those with acute cases of rheumatic fever as justifiably as the febrile cases, among which are cases of untreated pneumonia, measles, varicella, fever of undetermined origin, and acute pharyngitis. The untreated "controls" would then number 53 plus 50 plus 50 or 153 cases in which 58 plus 66 plus 58 or 182 cultures were taken. There were in this group 1.2 cultures per patient in comparison to 2.1 in the acute rheumatic cases. Should this slightly larger number of cultures per patient bring the results into question, a further comparison can be made with the convalescent rheumatic fever patients, both with and without therapy, who had a ratio of 3.3 cultures per patient with less than 25 per cent positive while there were 66 per cent positive in the children with acute rheumatic fever.

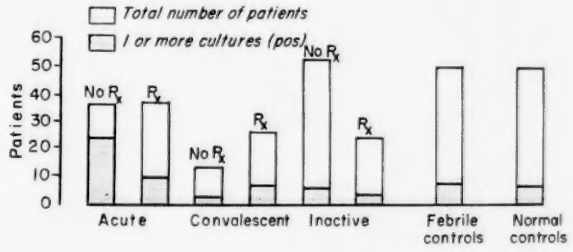

Fig. 1.—Bar graph illustrates total patients in each group, and shading indicates number of these patients with one or more cultures positive for the diplostreptococcus. R_x indicates therapy with antibiotic or chemotherapeutic medications in either therapeutic or prophylactic dosage.

It is noted also that the number of positive cultures decreases as an apparent effect of two factors: (1) the antibiotic medication, and (2) the passage of time from the date of onset. The antibiotic appears to be much more important in eliminating the positive cultures during the acute period than in the convalescent and inactive phases, since as seen in the tables the differences caused by therapy in the latter two groups are negligible. It may be, however, that the higher therapeutic dosages used during the acute phase are more effective in this regard than are the relatively low prophylactic dosages in the convalescent and inactive periods.

Our data were used in an attempt to clarify another question that has been repeatedly raised in regard to rheumatic fever, that is, whether acute and chronic rheumatic fever are actually two separate disease entities; that the

cultures obtained in the past by Cecil and others were derived from chronic cases which resembled the findings in rheumatoid arthritis. A bar graph (Fig. 2) shows the division of the cultures along a time axis extending from the date of onset to the end of the first year of the disease. This table shows that the majority of positive cultures was found during the first 30 days of disease.

Fifty of the organisms found were completely studied.[76] Forty-five of the 50 could be grouped, the majority (34 or 68 per cent) belonging both biologically and serologically to the enterococcus group. In the "probable" enterococcus group, 4 strains were serologically groupable with D serum but did not fulfill all the biologic characteristics, and 4 which were biologically so grouped did not show the serologic identification. A total then of 42 (or 84 per cent) did fall within the enterococcic group by one or both of these tests. The remaining 8 organisms showed 7 grouped as "A" serologically and one that was not serologically groupable but had the "A" characteristics biologically.[76]

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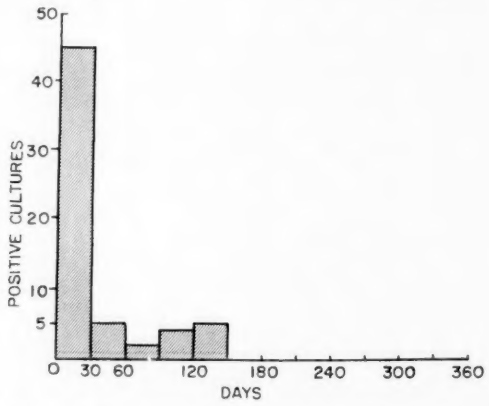

Fig. 2.—Duration of disease at the time of culture. Sixty-one positive cultures on rheumatic patients within one year of onset, illustrating that the majority of the positive cultures are obtained in cases in which less than 30 days had elapsed since the onset of the rheumatic attack.

Few of the organisms produced hemolysis by the tube test but several were slightly beta hemolytic upon horse blood agar plates. The tests for penicillin sensitivity showed 11 strains sensitive to less than 0.05 unit per cubic centimeter of penicillin G; 8 strains to less than 2.5 units; 4 additional strains were sensitive to less than 10 units; and the remaining 27 strains were resistant to more than 10 units per cubic centimeter of penicillin.

DISCUSSION

The last alternative which we previously listed, the possibility that an organism such as we have found may serve to continue the rheumatic fever which has been instigated by the Group A streptococcus seems worthy of further investigation.

The finding of this enterococcus-like organism in so high a percentage from the blood of patients with acute rheumatic fever suggests at least the possibility that this organism may be implicated in the disease process by virtue of the prop-

erties antigenic, enzymatic, or toxic which it shares with the Group A beta hemolytic streptococcus. A relationship in all of these factors has been frequently demonstrated by many workers. We have also been able to demonstrate crudely to our own satisfaction marked cross-reaction between these organisms and the Group A streptococcus using whole organisms as antigen in rabbits.

The percentage of positive cultures in the acute rheumatic patient which we found is also in close agreement with the percentages found by Cecil,[41] Callow,[53] Herry,[24] Freund,[31] and Suranyi.[39] Some of the common denominators in these studies which showed a high percentage of positives are: (1) prolonged period of incubation, (2) first subculture into a semiliquid medium, (3) a sufficient dilution of the blood to decrease any possible inhibiting effect that may be present in the blood itself, and finally (4), the fact that no medication (including salicylates) had been administered prior to the culture in the acute state.

It may also be said that the presence of a resistant variant of the Group A streptococcus or the organism which we have found, similar to that described in the recent literature on the P.P.L.O. forms, has not been ruled out by our work. This consideration may serve as an explanation for the prolonged period of incubation necessary, since this time seems to coincide with the interim required for the regeneration of the streptococcus from the "round bodies."

The questions which our findings raise in regard to the relationship of rheumatic fever to subacute bacterial endocarditis are of considerable importance to the clinical management of these two diseases. It appears at this time that we may be dealing with the same disease process in a host with differing responses of hypersensitivity and immunity.

It has been our own experience that immediate high dosage of penicillin given to a patient who is *unprotected* by salicylate or steroid premedication may provoke untoward and sometimes serious reactions. This in no way implies that penicillin should not be used in rheumatic fever or that it may not eventually eliminate the infection if used properly. In a similar instance of a "hypersensitivity" stage in another disease, namely, syphilis, penicillin may cause a fatal or very serious "Herxheimer reaction" in the secondary stages despite the fact that this antibiotic will finally bring about a complete cure of the disease itself.

This type of possible "rheumatic shock" reaction has been described by others.[57-60] It has also been our impression in reviewing the literature that the high incidence of immediate reactions to chemotherapeutic and antibiotic agents in acute rheumatic fever may indeed be evidence for this type of reaction. The possible sudden flooding of the circulation with bacterial antigen during the acute rheumatic "hypersensitive" state may be the cause rather than the specific drug itself. On numerous occasions exposure to the same drug or antibiotic during the inactive or convalescent stage in the same patients will provoke no such reaction.

In conclusion, it may very well be found, however, that we have succeeded only in the demonstration of an incidental bacteremia during the clinical course of acute and chronic rheumatic fever. This does not appear to be likely in view of past work, but nevertheless the presence of these organisms requires explanation, whether or not there is an etiological relationship.

SUMMARY

1. We have obtained 385 blood cultures from 185 patients with rheumatic fever in various stages. In patients who had received no therapy, a diplostreptococcus was found in 66 per cent in the acute stage, 22 per cent in the convalescent stage, and 10 per cent in the inactive stage. One hundred and twenty-four control cultures were drawn from 100 age-matched and untreated patients, half of whom had nonfebrile illness and half of whom had febrile illnesses of various types. The percentage of positive cultures, including staphylococcal contaminants, was 14 per cent in the febrile controls and 12 per cent in the nonfebrile controls. The high percentage of positive cultures in the rheumatic patients appeared to be related both to the acuteness of the disease and the absence of antibiotic or salicylate medication.

2. The organism obtained has been identified as being most closely related to the "enterococcus" group of streptococci, most of the organisms belonging to Group D.

3. The suggestion is made that the presence of these organisms in the blood stream may be an indication of their importance in the pathogenesis of the rheumatic process initiated by the Group A beta hemolytic streptococcus.

We would like to express our appreciation for invaluable help and guidance to Drs. Luis Mabilangen, Gershon Hait, George Vrla, and Gunther Bucheleres, Fellows in Cardiology at the Cook County Children's Hospital; Dr. Benjamin Gasul, Chief of the Children's Cardiac Service at the Cook County Children's Hospital; Dr. John Tobin, Director of the Cook County Blood Bank and Mr. Raymond Coles of his Staff; Dr. F. R. Kutner, Chicago Medical School; and Dr. Heyworth Sanford, Head of the Department of Pediatrics of the University of Illinois Medical School. To the late Dr. Henry Poncher, we gratefully acknowledge the stimulation of this work.

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CURRENT STATUS OF AMPHOTERICIN B IN THE TREATMENT OF THE SYSTEMIC FUNGUS INFECTIONS

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AMPHOTERICIN B is a new antifungal antibiotic which was isolated from an unidentified species of Streptomyces, originally grown from soil samples obtained from the Orinoco River region of Venezuela. Its chemical and physical properties were early characterized by Vandeputte[1] and later in more detail by Dutcher and associates.[2] It is a member of a larger family of closely allied polyene antifungal agents which include amphotericin A, rimocidin, nystatin, candicidin, ascosin, trichomycin, fungichromin, and filipin.[1,2] A tentative empirical formula has been assigned to it of $C_{46}H_{73}NO_{20}$. In vitro, amphotericin B inhibits a wide variety of pathogenic and nonpathogenic fungi in concentrations ranging from 0.5 to 12.5 mcg. milliliter,[3,4] including *Blastomyces dermatitidis, Blastomyces brasiliensis, Candida albicans, Cryptococcus neoformans, Histoplasma capsulatum,* and *Coccidioides immitis.* The acute and chronic toxicity of amphotericin B is relatively low when administered intraperitoneally in mice.[4] The drug favorably influences the course of experimental infections with *Canadida albicans, Cryptococcus neoformans, Histoplasma capsulatum,* and *Coccidioides immitis.*[4-9] In experimental animals biologic cures have occurred when the drug is administered concomitantly with or shortly after inoculation. In the majority of instances, however, where the drug is withheld until the infection is well established, health is restored to a varying degree, with a resulting prolongation of life, but it is still possible to culture the organisms from various organs.

These promising laboratory studies stimulated detailed evaluation of amphotericin B for the treatment of fungus infections in man.

This research was supported in part by a grant from the Squibb Institute for Medical Research, New Brunswick, N.J., who also supplied the Amphotericin B.

This paper summarizes our experience to date, together with a review of the literature concerning the clinical effectiveness of amphotericin B in the treatment of the systemic mycoses.

ADMINISTRATION OF AMPHOTERICIN B

Oral.—Data obtained from early animal studies indicated that amphotericin B was poorly absorbed from the gastrointestinal tract but sufficiently absorbed to influence favorably the course of the infection.[4,6] Accordingly, 5 normal adult men were given amphotericin B orally in doses of 2 to 8 Gm. daily. Blood levels were determined at frequent intervals by the method described by Tarbet and Sternberg.[10] On repeated sampling only small amounts of amphotericin B could be detected in the sera of these individuals. The highest levels were found in those individuals receiving a total dose of 10 Gm. over a 30-hour period. The levels varied from 0.7 to 3.2 mcg. per milliliter. Two patients, one with coccidioidomycosis and one with meningitis due to *Cryptococcus neoformans*, were given amphotericin B orally in doses as high as 16 Gm. a day.[6] A maximum level of 3.5 mcg. per milliliter was detected in the serum of the patient with cryptococcosis at the time she was receiving 16 Gm. of amphotericin B per day orally. Similar levels were observed in the serum of the patient with coccidioidomycosis when he was receiving 10 Gm. of amphotericin B orally per day.

The patient with cryptococcosis was treated for 16 days with no clinical evidence that amphotericin B influenced the course of infection and succumbed at the end of this period of time. The patient with coccidioidomycosis was treated over a period of 2 months with no improvement. Evidence of toxicity was not discernible in any patient receiving amphotericin B orally, even in the one patient who received dosages as high as 16 Gm. per day.[6]

On the basis of these data it was concluded that amphotericin B was poorly absorbed from the gastrointestinal tract and that this route of administration offered little promise with the then currently available oral preparation. Louria[11] has recently studied four different oral preparations of amphotericin B in regard to their absorption, distribution, and excretion in man. He concluded that oral amphotericin B was poorly absorbed, as only low blood levels were obtained. Littman, Horowitz, and Swadey[12] were unable to find assayable levels following the oral administration of amphotericin B. Utz and associates[13] treated 13 patients with systemic mycoses including blastomycosis, coccidioidomycosis, cryptococcosis, and histoplasmosis. Four oral preparations of amphotericin B were evaluated. Maximum dosages of 5 Gm. daily were given. Of the 13 one showed apparent recovery and 3 subjective improvement, and the remainder showed no improvement. Very low blood levels were found and it was concluded that these oral preparations were poorly absorbed from the gastrointestinal tract. Therefore, they felt that oral therapy would be of limited usefulness in the treatment of the systemic mycoses except in those instances where a patient was infected with a strain of fungus sensitive to low concentrations of amphotericin B.

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Intramuscular.—Studies directed toward evaluating the feasibility of employing the intramuscular route in the administration of amphotericin B revealed that when dosages in the range of 25 to 50 mg. were injected intramuscularly with or without such adjuvants as procaine, hyaluronidase, and hydrocortisone there resulted painful, indurated tumescences at the injection sites which necessitated discontinuation of therapy, and this route of administration was therefore abandoned.

Intravenous.—This route has proved to date to be the most effective means by which amphotericin B can be administered. The drug is highly insoluble in aqueous solutions and earlier intravenous preparations consisted of suspensions of amphotericin B. A more soluble form, utilizing sodium desoxycholate, has recently become available for clinical use. This preparation, when reconstituted with 5 per cent glucose in water, appears clear to the eye. However, it demonstrates a Tyndall effect, thus suggesting not a true solution but a colloidal dispersion with particles smaller than bacteria.[14] Higher titers of the drug in the serum appear to be obtainable with this preparation.[15] The drug is administered intravenously in 500 to 1,000 c.c. of 5 per cent glucose in water over a 6-hour period. The initial dose is usually in the range of 5 to 10 mg. per day with daily increments of 5 to 10 mg., depending on the patient's tolerance of the drug. Once a dosage level of 0.7 to 1.4 mg. per kilogram per day is reached in the adult (50 to 100 mg. per day) an attempt is made to maintain it. Recent studies suggest that interrupted therapy may be just as effective as daily therapy apparently due to storage and subsequent release of the drug into the circulation, although higher blood levels are achieved with daily than with interrupted therapy when the solubilized form of the drug is used.[15] Adjustments of the dosage including complete cessation of the drug for short periods of time, administration on alternate days, and returning to lower dosages, are employed as necessitated by the patient's reactions. Dosages of more than 100 mg. of amphotericin B intravenously per day have been tolerated by adults for short periods of time, but, in our experience, toxic manifestations soon necessitate the reduction of this daily dosage.

The drug has also been administered, under special circumstances, intrathecally, intra-articularly, intrathoracically, subcutaneously, and by the intrapulmonary route.

Dosages as high as 1 mg. every other day have been employed intrathecally with no untoward side effects. This level was arrived at by gradual increments from an initial dose of 0.1 mg. Two patients have been thus treated, one with cryptococcal meningitis and one with coccidioidal meningitis. The amphotericin B powder is reconstituted in sterile water and the necessary quantity of amphotericin B is added to 2 to 3 c.c. of spinal fluid which is reinjected intrathecally.

Amphotericin B, dissolved in distilled water with streptokinase and streptodornase, has been injected intra-articularly[12] in doses as high as 25 mg. This was well tolerated when injected on alternate days.

Pulmonary instillation of amphotericin B in the form of an aerosol spray prepared with 5 mg. of amphotericin B in 1 ml. of distilled water has been successfully employed on an every 6-hour schedule.

In dosages of 3 mg. dissolved in sterile distilled water the drug has been injected into the thoracic cavity with no untoward effects. However, an accidental injection of 15 mg. of amphotericin B into the thoracic cavity resulted in a severe febrile but nonfatal reaction. We have treated one patient with a large, open, postpneumonectomy wound with compresses of 50 mg. of amphotericin B in 1,000 c.c. of 5 per cent glucose in water, but these produced moderate inflammation and were discontinued.

Costello, DeFee, and Littman[16] successfully treated one case of chromoblastomycosis by local infiltration with 20 to 25 mg. of amphotericin B admixed with 2 per cent procaine.

CASE MATERIAL AND REVIEW OF THE LITERATURE

To date we have treated with intravenously administered amphotericin B 22 patients with various systemic mycoses, either under direct observation or in cooperation with other physicians in the community. All patients were hospitalized and the following baseline studies were obtained whenever possible before instituting therapy: complete blood count, urinalysis, chest film and other appropriate x-rays, serologic tests where applicable, blood urea nitrogen, liver function tests, and spinal fluid examinations where applicable. These studies were repeated at intervals during the course of therapy.

Amphotericin B was administered in courses varying from 3 weeks to 4 months in duration. The patients have been followed for periods varying from 5 months to 2 years.

Tables I and II detail the patients treated. Table III summarizes the diseases treated and the results observed to date. Table IV summarizes the in vitro sensitivity of various pathogenic fungi to amphotericin B.

Coccidioidomycosis.—Five of the 14 patients with coccidioidomycosis had coccidioidal meningitis. Three of these 5 patients showed improvement from the clinical standpoint by clearing of sensorium, disappearance of headache, improvement in neurologic findings, cessation of nausea and vomiting, improved appetite, weight gain, disappearance of fever, and—in one instance—return to gainful employment. Although the spinal fluid findings have also improved in all of these 3 patients, some laboratory abnormalities have, ominously, persisted, including increased protein, pleocytosis, and elevated pressure. One of the 3 patients has recently relapsed, approximately 7 months after cessation of therapy, and further treatment is now contemplated. Contact has been lost with one patient, and the fifth patient succumbed after 7 weeks of treatment with an early preparation of a suspension of amphotericin B.

Six of the remaining 9 cases of disseminated coccidioidomycosis, which involved principally bone, skin, and lung, have shown clinical evidence of improvement while under direct observation. This has included an early increased feeling of well-being, improved appetite, gradual weight gain, increased strength, decreased fever, stabilization or reduction in size or complete resolution of pulmonary infiltrates, healing of draining sinuses, and partial or complete healing of cutaneous lesions.

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TABLE I. SYSTEMIC MYCOSES TREATED WITH AMPHOTERICIN B

PATIENT, AGE, RACE, AND SEX	DIAGNOSIS	SKIN TEST	COMPLEMENT FIXATION	PRECIPITIN	DOSAGE OF AMPHOTERICIN B	DURATION OF TIME	RESULTS
1. D. C. 44 yr. W. M.	Possible coccidioidal meningitis	2+ 1:100	Serum 1+ 1:16, spinal fluid negative	Negative	50 mg. IV every day	2 mo.	Remission of symptoms of headache and vomiting
2. T. L. 48 yr. W. M.	Coccidioidal meningitis	Negative 1:100	Serum 1+ 1:16, spinal fluid 1+ 1:8	Negative	10 to 50 mg. IV every day 50 mg. IV every day	2 wk. 6 wk.	Complement fixation tests of spinal fluid after 8 wks. treatment 1+ 1:16, afebrile, mentally alert, discharged from hospital
3. C. S. 26 yr. W. M.	Coccidioidal meningitis	Negative 1:100	Serum 3+ 1:16	Negative	50 mg. IV every day 0.1 to 1 mg. intrathecally twice weekly	10 wk. 7 wk.	Some improvement in laboratory findings, spinal fluid protein, cells and pressure decreased, over-all condition unchanged
4. R. B. 33 yr. W. M.	Coccidioidal meningitis	Negative 1:100	Serum 2+ 1:8	Negative	5 to 50 mg. IV every day	5 mo.	Clinically well, skin test 1+ 1:10
5. S. C. 27 yr. American Indian M	Coccidioidal meningitis	Negative 1:100	Serum 2+ 1:16, spinal fluid 4+ 1:4	Negative	Suspension 1.5 mg./Kg. every day	7 wk.	Expired
6. A. L. 12 yr. Mexican F	Coccidioidal granuloma of radial head and left midtarsal area	—	Serum 1+ 1:256	Negative	50 mg. IV every day	3 wk.	Healing of sinus tract of foot, improvement in sinus tract of arm after radial head resection
7. G. F. 6 yr. Mexican F	Possible coccidioidal granuloma left ankle	Positive 1:100	Serum 2+ 1:4	Negative	15 mg. IV (1 mg./Kg.) every day	10 days	No improvement
8. R. D. 33 yr. N M	Coccidioidomycosis with granuloma of neck	4+ positive 1:100	Serum 4+ 1:32	4+ 1:10	50 mg. IV every day, or every other day	2 mo.	Clearing of lung fields, cessation of cough, afebrile, increased weight and strength, no adenopathy, granuloma of neck healed

TABLE I. SYSTEMIC MYCOSES TREATED WITH AMPHOTERICIN B—CONT'D

PATIENT, AGE, RACE, AND SEX	DIAGNOSIS	SKIN TEST	COMPLEMENT FIXATION	PRECIPITIN	DOSAGE OF AMPHOTERICIN B	DURATION OF TIME	RESULTS
9. S. D. 36 yr. N M	Disseminated coccidioidomycosis with destruction of several carpal bones	Positive 1:1000	Serum 3+ 1:128	Negative	25 to 140 mg. IV every day	4 mo.	Complement fixation dropped to 3+ 1:32, little clinical change
10. J. H. 46 yr. W M	Disseminated coccidioidomycosis with skin lesions	Negative 1:100	Serum 2+ 1:32	4+ 1:40	50 mg. IV every day	3 mo.	Complement fixation dropped to 2+ 1:16, precipitin dropped to 0, afebrile, no clinical evidence of recurrence, complete healing of skin lesions, lung infiltrate unchanged, now working
11. C. B. 55 yr. W M	Disseminated coccidioidomycosis with coccidiodal lymphadenitis	Negative 1:100	Serum 1+ 1:4	4+ undiluted	50 mg. IV every day	25 days	Complement fixation 2+ 1:16, regression of lung lesions, clinically well and returned to work
12. B. A. 23 yr. W M	Disseminated coccidioidomycosis and pleurocutaneous fistula	Negative 1:100	Serum 2+ 1:256	Negative	5 to 15 Gm. per os every day	3½ mo.	No change
13. R. R. 2½ yr. W M	Pulmonary aspergillosis with mass in neck and draining thoracic sinus				1 to 10 mg./Kg. IV every day 1 Gm. per os every day	3 mo. 3 mo.	Partial healing of draining sinus of chest, partial clearing of lung infiltrate, general clinical improvement
14. R. T. 57 yr. W M	Pulmonary aspergillosis				8.4 to 40 mg. IV every day 50 mg. IV every day	9 days 6 days	Therapy discontinued because of phlebitis, no improvement at that time
15. R. E. 48 yr. W M	*Candida parakrusei* infection of eye after corneal transplant				5 to 10% solution topically 30 to 80 mg. IV every day	26 days 7 days	Candida infection cleared
16. T. H. 29 yr. W F	Cryptococcal meningitis				0.25 mg./Kg. 0.50 mg./Kg. 0.75 mg./Kg. 1.00 mg./Kg. IV every day	5 days 5 days 3 days 8 days	Spinal fluid cultures became negative March 26, drug started April 13, returned home, clinically fairly well

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17. M. S. 30 yr. W F	Cryptococcal meningitis				10 to 16 Gm. per os every day	16 days	Expired
18. L. R. 58 yr. W M	Cryptococcal meningitis				15 to 50 mg. IV every day 50 mg. IV every day	9 days 15 days	Expired
19. E. J. C. 40 yr. W M	Disseminated coccidioidomycosis	Positive 1:100	Serum 2+ 1:32		5 to 50 mg. IV every day 45 to 60 mg. IV every day	10 days 26 days	Marked reduction of swelling dorsum right hand and scrotal nodules, symptomatically improved, complement fixation unchanged, returned to work
20. W. M. 42 yr. W M	Cryptococcal meningitis				5 to 50 mg. IV every day 50 mg. IV every day	7 days 39 days	Clinically well with disappearance of headache and clearing of sensorium
21. A. S. 26 yr. N M	Disseminated coccidioidomycosis with bone and skin involvement	Negative	Serum 2/22 1:2048 5/1 1:16000 6/6 1:4096 7/10 1:8192		5 to 50 mg. IV every day 50 mg. IV every day	8 days 3½ mo.	Gained 25 lbs. (131 to 156), increased appetite, strength, elevated hemoglobin from 8 to 13.6 Gm., healing of abscesses low back and closure sinus tract from low back to left femoral head area
22. T. M. 50 yr. W M	Mycetoma (Madura foot) due to *Monosporium apiospermum*				5 to 50 mg. IV every day 50 mg. IV every day	10 days 13 days	Decreased drainage from nodules on foot, otherwise no change
23. J. P. 23 yr. N M	Cryptococcal meningitis				5 to 40 mg. IV every day 50 mg. IV every day 0.1 to 1 mg. intrathecally every other day	5 days 60 days 1 mo.	Dramatic clinical improvement, spinal fluid cultures negative at one month posttreatment
24. W. S. 62 yr. W M	North American blastomycosis				12.5 to 40 mg. IV every day 50 to 75 mg. IV every day	4 days 18 days	Cutaneous lesions healed, epididymitis cleared, urine culture for *B. dermatitidis* negative 2 weeks posttreatment

TABLE II.

PATIENT, AGE, RACE, AND SEX	TOXICITY	REMARKS	DRUG LEVELS[33]
1. D. C. 44 yr. W M	Increase of BUN, nausea	Patient had had bilateral upper lobectomies for pulmonary coccidioidomycosis, and subsequently developed headache and morning vomiting, with elevated spinal fluid pressure, increased protein, and cells, cultures, complement fixation, and precipitin tests of spinal fluid all negative; patient has been asymptomatic for approximately 10 months since discharge from hospital	
2. T. L. 48 yr. W M	Chills, fever, increase in BUN, and drop in hematocrit from 47 to 35	Seven months after treatment relapsed, retreatment is contemplated	
3. C. S. 26 yr. W M	Vomiting following IV administration (vomiting also part of clinical picture prior to treatment)	Transferred to U.S.V.A. Hospital in Houston, Texas; further contact lost	Spinal fluid: 0.20 to 0.56 mcg./ml.
4. R. B. 33 yr. W M	Malaise, tremor, and back pain	Has returned to gainful employment	
5. S. C. 27 yr. American Indian M			Serum 1.55 to 2.65 mcg./ml. Spinal fluid: 0 to 0.74 mcg./ml.
6. A. L. 12 yr. Mexican F	Nausea, vomiting, fever		
7. G. F. 6 yr. Mexican F	Chills, fever, nausea	Diagnosis of coccidioidomycosis not confirmed by culture	
8. R. D. 33 yr. N M	Nausea, vomiting, fever. BUN increased from 6 to 26	Complement fixation rose to serum 2+ 1:256.	

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9. S. D. 36 yr. N M	Occasional low-grade fever	Hematocrit fell from 51 to 45, BUN rose from 19 to 44, later dropped to 10 while still on drug	Serum 1.2 mcg./ml.
10. J. H. 46 yr. W M	Nausea for first 10 doses, none thereafter, mild persistence of backache, fever, and vomiting for first 13 doses, none thereafter	No rise in BUN, prophylactic aspirin and antihistamines did not prevent fever with drug administration	
11. C. B. 55 yr. W M	Nausea, vomiting, and fever	BUN rose from 15 to 28	Serum 3.65 mcg./ml. Urine 5.0 mcg./ml.
12. B. A. 23 yr. W M	None observed	Refused IV medication	Serum 0.0 mcg./ml.
13. R. R. 33 yr. N M	Vomiting	Patient had hypergammaglobulinemia and history of many previous infections	Serum 0.53 to 1.82 mcg./ml. Spinal fluid 0.00 mcg./ml. Urine 1.05 to 1.41 mcg./ml.
14. R. T. 57 yr. W M	Hemoglobin dropped from 15.5 to 13.2 Gm., chills, fever	Current status unknown	
15. R. E. 48 yr. W M	None	Grafts sloughed and eye lost	
16. T. H. 29 yr. W F	Vomiting, fever, rise in BUN	While on drug had 4 grand mal seizures and became semicomatose, now home and clinically fairly well	Serum 0 to 2.2 mcg./ml. Spinal fluid 0
17. M. S. 30 yr. W F	None		
18. L. R. 58 yr. W M	Chills, fever, nausea, vomiting	Underlying pathology of multiple myeloma preceded onset of cryptococcal meningitis, course complicated by a *Proteus mirabilis* septicemia	

TABLE II—CONT'D

PATIENT, AGE, RACE, AND SEX	TOXICITY	REMARKS	DRUG LEVELS[33]
19. E. J. C. 40 yr. W M	Hemoglobin dropped from 14 to 11.1 Gm.	Has remained clinically well to date and returned to work	
20. W. M. 42 yr. W M	BUN rose from 16 to 28 mg. per cent, chills, fever from 100 to 102° F., hemoglobin dropped from 18 to 10 Gm.	Spinal fluid cells *Before* 1,100 *After* 116 protein 1+ Pandy low unchanged sugar 400 normal pressure 90	
21. A. S. 26 yr. W M	Chills, fever, nausea, decreased with progressive administration, rise in BUN to 35 mg. per cent	Excellent clinical improvement despite poor serologic response	
22. T. M. 50 yr. W M	Nausea, vomiting, chills, fever, BUN rose to 42.8 mg. per cent	No significant improvement	
23. J. P. 23 yr. N M	Nausea, chills, vomiting, fever		
24. W. S. 62 yr. W M	Chills, nausea, fever, vomiting, hemoglobin dropped from 15.5 to 13, creatinine rose from 1.2 to 2.3	Therapy stopped because of localized phlebitis	

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No improvement occurred in 2 patients who had coccidioidal osteomyelitis and who were given amphotericin B intravenously. No improvement occurred in one patient who was given amphotericin B orally in doses as high as 16 Gm. per day.

TABLE III. RESULTS OF AMPHOTERICIN B IN 24 PATIENTS WITH SYSTEMIC MYCOSES

	TOTAL	IMPROVED	UNCHANGED	WORSE	UNKNOWN
Disseminated coccidioidomycosis: Meningitis	5	2	1	1	1
Bone, skin, lung	9	6	3*		
Cryptococcal meningitis	5	3		2*	
Pulmonary aspergillosis	2	1	1		
Candida parakrusei infection of eye	1	1			
Mycetoma due to *Monosporium apiospermum*	1		1		
North American blastomycosis	1	1			
Total	24	14	6	3	1

*One of these patients received only oral amphotericin B.

TABLE IV. THE EFFECT OF AMPHOTERICIN B ON THE GROWTH OF VARIOUS PATHOGENIC FUNGI IN ASPARAGINE BROTH

	MICROGRAMS OF AMPHOTERICIN B* PER MILLILITER OF MEDIUM								
	0.0	0.5	1.0	2.0	5.0	10.0	20.0	50.0	100.0
Coccidioides immitis (strain 1)	3†	1	1	1	1	1	1	1	1
C. immitis (strain 2)	3	1	1	1	1	1	1	1	1
C. immitis (strain 3)	3	1	1	1	1	1	1	1	1
Candida albicans (strain 1)	3	1	1	1	1	1	1	1	1
C. albicans (strain 2)	3	1	1	1	1	1	1	1	1
C. albicans (strain 3)	3	1	1	1	1	1	1	1	1
Cryptococcus neoformans	3	1	1	1	1	1	1	1	1
Sporotrichum schenkii	3	3	3	3	3	3	3	3	3
Nocardia asteroides	3	3	3	3	3	3	3	3	3
Blastomyces dermatitidis	3	1	1	1	1	1	1	1	1
Histoplasma capsulatum	3	1	1	1	1	1	1	1	1
Trichophyton rubrum	3	1	1	1	1	1	1	1	1
T. mentagrophytes	3	2	1	3	1	1	1	1	1
Microsporum canis	3	3	1	1	2	1	2	1	1
M. audouini	3	1	1	1	1	1	1	1	1

*Amphotericin B Lot #HA 596A.

†Gross evaluations were made at 10 days, and the amount of growth was rated as follows: *3* represents growth of the organisms in the control tubes; *2* represents more than minimal growth, but less than the amount of growth observed in the control tubes; *1* represents no or minimal perceptible growth.

Other investigators have noted a favorable response in coccidioidomycosis treated with amphotericin B. Fiese[17,18] has reported his experience in the treatment of 3 patients with disseminated coccidioidomycosis, all of whom underwent apparent remission. One patient with a coccidioidal granuloma of the face of 7 years' duration was treated with 2.4 Gm. of amphotericin B by mouth daily to a total dosage of 200 Gm., with clinical and laboratory evidence of improvement. A relapse occurred subsequently in this patient, which again subsided, but more slowly, when given amphotericin B therapy.[18,19] Littman[12,20] has treated 3 patients with disseminated coccidioidomycosis and one patient with pulmonary coccidioidomycosis with cavitation. One of these patients, with coccidioidal osteomyelitis, received a total of 222 Gm. of amphotericin B orally over a 24-day period, with no improvement. The patient was subsequently given a total of 4,700 mg. of amphotericin B intravenously over a 118-day period, with marked clinical improvement. His complement fixation titer dropped from 1:32 to 1:16. Another patient, a 23-year-old Negro man with disseminated coccidioidomycosis, with left knee joint involvement, received 2,075 mg. of amphotericin B intravenously in 32 infusions over a 19-week period, and 800 mg. of amphotericin B was injected intra-articularly in 23 doses. He became completely asymptomatic. Three weeks after discharge the patient relapsed and received a second course of amphotericin B intravenously over a 42-day period for a total of 1,206 mg. in 16 infusions, with complete healing of sinus tracts and conversion to cultural negativity. His complement fixation titer for coccidioidomycosis eventually showed a drop from 1:512 to 1:128. His skin test, however, remained negative.

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Two other patients were briefly reported, one with disseminated coccidioidomycosis with skin lesions and one with pulmonary coccidioidomycosis with cavitation. Both responded to amphotericin B administered intravenously.

Utz and associates[13] treated 2 patients, one with disseminated coccidioidomycosis and one with pulmonary coccidioidomycosis, with amphotericin B orally in doses of 2.4 to 5 Gm. per day. The first patient expired after 105 days of therapy. The second patient showed no change after 180 days of therapy and was subsequently given 15 to 20 mg. of amphotericin B intravenously daily for 35 days, with no improvement.

Williams and Skipworth[21] treated a single patient with disseminated coccidioidomycosis, presenting as a granulomatous lesion of the left cheek, with 3 Gm. of amphotericin B orally daily for 4 weeks, with no improvement. The patient was then given 50 to 75 mg. of intravenous amphotericin B daily or every other day to a total of 1,610 mg. over a 6-week period. His complement fixation titer decreased from 4 plus at 1:128 to 3 plus at 1:32. The patient became asymptomatic and gained weight, and the lesion regressed. However, biopsy at the conclusion of treatment revealed the presence of a coccidiodal spherule in one section.

Klapper, Smith, and Conant[22] report a case of a 34-year-old white woman with a 10-year history of disseminated coccidioidomycosis involving bone and muscle, with multiple draining sinuses. The patient was given 1 Gm. of amphotericin B orally four times a day. Response was rapid and complete healing oc-

curred within 3 months. However, medication was continued for a total of 14 months to avoid relapse. Complement fixation titer 6 months after treatment was completed had decreased from 1:64 to 1:16.

No subjective side effects were noted.

Cryptococcosis.—Amphotericin B has been given either orally or intravenously to 5 patients with cryptococcal meningitis. The one patient who received the oral preparation, in doses as high as 16 Gm. per day, for a total period of 16 days, showed no evidence of alteration in the course of the disease and succumbed. Another patient succumbed after 24 days of intravenous amphotericin B therapy totalling 1,020 mg. This patient had an underlying multiple myeloma and his course was complicated by a *Proteus mirabilis* septicemia. *Cryptococcus neoformans* was cultured from the meninges at post mortem and virulence was proved by guinea pig inoculation.

The remaining 3 patients all have shown moderate-to-marked clinical improvement including clearing of sensorium, disappearance of headache, improvement in neurologic abnormalities, and improvement in general clinical condition. In all of these patients the spinal fluid cultures have remained negative, pleocytosis has returned toward normal, and the spinal fluid sugar and hydrodynamics have reverted toward normal. However, some abnormalities still exist in the spinal fluid of all 3 patients. None of these patients has been observed for a sufficient length of time to make a definitive statement regarding the final outcome. The longest patient follow-up has been 15 months.

Applebaum and Shtokalko[23] treated one patient with cryptococcal meningitis for 5 weeks with oral amphotericin B in dosages as high as 8 Gm. daily with no response. They then administered the intravenous preparation in doses of 100 mg. on alternate days for 5 weeks. On discharge from the hospital the patient was described as being in good physical condition and free of any signs or symptoms referable to the central nervous system. Follow-up 7 months later found the patient in the same satisfactory state.

Furcolow and his associates, in a series of papers,[24-26] report 10 cases of cryptococcal meningitis treated with amphotericin B intravenously in doses of 50 to 100 mg. per day or every other day to a total dosage of from 1.4 to 3.7 Gm. in the 8 surviving patients.

Two moribund patients expired after short courses of therapy. The 8 surviving patients had been followed at the time of writing for periods of 2 to 14 months. Of these 8, 7 showed consistent sterility of the spinal fluids on culture for *Cryptococcus neoformans.* Two of these patients returned to normal activities, one was asymptomatic, 3 were improved, one relapsed, and one was unchanged clinically. The authors concluded that amphotericin B seemed to be the most promising agent available for the treatment of cryptococcal meningitis.

Utz and his colleagues[13] treated 5 patients with cryptococcal meningitis with amphotericin B orally in doses as high as 5 Gm. daily. No objective signs of improvement occurred but 3 of the patients had marked subjective improvement. One additional patient, in whom the disease was limited to soft tissue and bone, recovered and was apparently well one year after treatment. Three

of the patients subsequently received daily dosages of amphotericin B intravenously, ranging from 10 to 40 mg. per day over periods of 14 to 100 days. No change occurred in these 3 patients. The authors explain the lack of effectiveness of amphotericin B in patients with cryptococcal meningitis as due in part to the low spinal fluid levels achieved even with intravenous therapy.

Vogel and Crutcher[15] describe a case of cryptococcal meningitis treated with amphotericin B in daily dosages intravenously of 1 to 1.5 mg. per kilogram for about 3½ months with clinical improvement and reversion of the spinal fluid to cultural negativity.

Fitzpatrick, Rubin, and Poser[27] report one case of cryptococcal meningitis treated with oral amphotericin B in doses of 2 Gm. per day over a 5-day period at the end of which time the patient succumbed. They also treated 2 patients with chronic cryptococcal meningitis—one with combined oral and intravenous therapy and one with oral, intramuscular, intravenous, and intrathecal therapy.

The first patient received amphotericin B in doses of 50 mg. per day intravenously for 2 weeks and 100 mg. intravenously every other day for 8 weeks. She then received amphotericin B orally in doses of 4 Gm. per day for an additional 2 months. She became clinically well and the spinal fluid returned to normal and, upon follow-up study 9 months after discontinuation of therapy, showed no evidence of recurrence. The second patient received amphotericin B orally for 2 weeks with no apparent effect. He then received the drug intramuscularly for one week and then intravenously in doses of 100 mg. every other day for 3 months. Following this he received the drug intrathecally in doses of 1 mg. every other day for 10 days. The patient showed some improvement and the spinal fluid reverted to cultural negativity.

The authors concluded that amphotericin B was a practical and effective drug for the treatment of cryptococcal meningitis.

Crounse and Lerner[28] report a case of cutaneous cryptococcosis treated initially with 3 to 12 Gm. of amphotericin B orally daily over a 10-week period, to a total dose of 215 Gm., with no visible therapeutic or toxic effect. The patient was then given a course of amphotericin B intravenously, consisting of 1 Gm. of the drug given over an 18-day period, with remarkable regression of the lesions and conversion to cultural negativity. However, the patient relapsed in the ensuing 2 months and cultures again became positive. He was therefore again treated with a total of 920 mg. of amphotericin B intravenously over a 13-day period. Again there was rapid regression of the cutaneous lesions and reversion to cultural negativity. Three weeks later the patient developed a pneumonitis, with no *Cryptococcus neoformans* culturable from the sputum, and a return of skin lesions ensued. He was re-treated with 30 intravenous infusions of amphotericin B of 20 to 75 mg. per day. The skin again improved. The patient at this time is still under treatment.

North American Blastomycosis.—Our experience with North American blastomycosis has been limited to the treatment of one patient with genitourinary and cutaneous involvement with the favorable immunologic picture of a negative complement fixation test and a positive skin test. The patient received amphotericin B intravenously over a 22-day period to a total dose of 880 mg., with com-

plete healing of the cutaneous lesions and disappearance of *Blastomyces dermatitidis* from the urine. Follow-up has been too short as yet to allow final evaluation in this case.

Utz and associates[13] report 2 cases of blastomycosis treated with amphotericin B. The first patient, with pulmonary blastomycosis, received 5 Gm. daily orally for 28 days, with no improvement. He was then given 10 to 15 mg. daily intravenously for 8 days and the sputum became negative and had remained so for 6 weeks at the time of writing. The other patient had extensive osteomyelitis of the pelvic bones and cutaneous and soft tissue involvement. Following treatment with amphotericin B intravenously the sacral abscess became culturally negative, the wound healed, the epididymitis and cellulitis cleared, and the patient gained weight.

Harrell and Curtis[29] have recently reported their experience in the treatment of 4 male patients with severe systematized stilbamadine-resistant North American blastomycosis with amphotericin B. Prior to treatment all 4 patients had negative blastomycin skin tests and had positive complement fixation tests for blastomycosis, thus exhibiting the most unfavorable immunologic status. The patients received from 500 to 1,000 mg. of amphotericin B administered intravenously in daily doses of 50 mg. suspended in 1,000 c.c. of 5 per cent dextrose in water for periods varying from 20 to 30 days. There was complete healing of the cutaneous lesions within 3 weeks after the institution of amphotericin B therapy. There was also apparent disappearance of the causative organism from the sputum and/or skin in all 4 cases. The authors felt that the rapid response to amphotericin B therapy was encouraging, but they warned that, although all patients had remained free of clinically detectable disease at the time of writing, further time must elapse before cure can be considered as having been achieved.

Histoplasmosis.—We have had no experience in the treatment of histoplasmosis with amphotericin B.

Acute pulmonary histoplasmosis: Rubin, Lehan, and Furcolow[30] described one case of acute pulmonary histoplasmosis treated with amphotericin B in a dose of 4 Gm. orally for 6 days, subsequently increased to 9.6 Gm. orally per day for 2 days, and then decreased to 4 Gm. orally per day for 22 days. Beginning with the eleventh day of therapy amphotericin B was concomitantly administered intravenously in doses of 50 mg. every day or every other day to a total of 16 days at 50 mg. per day. This resulted in prompt reduction of temperature, clinical improvement, and rapid resolution of the pulmonary infiltrate. This suggested to the authors some possibility of a therapeutic effect of amphotericin B.

Lehan and colleagues[24] have recently presented their findings in the use of amphotericin B in the treatment of histoplasmosis. They treated 6 cases of progressive disseminated histoplasmosis and 6 cases of chronic progressive pulmonary histoplasmosis, and gave a preliminary report on the case of severe, nonfatal histoplasmosis later reported in detail by Rubin, Lehan, and Furcolow. These patients were treated with both the oral and intravenous preparations of amphotericin B.

Chronic progressive pulmonary histoplasmosis: Of the 2 cases treated with prolonged amphotericin B therapy orally, only one showed sterilization of the

sputum but both showed clinical improvement and slight-to-moderate x-ray changes. The remaining 4 were treated with both oral and intravenous amphotericin B, and, in all cases, clinical and x-ray improvement and sterilization of the sputum were achieved. In only one case, however, was cavity closure obtained.

Oral doses were as high as 8 Gm. a day and temporary improvement of several cases indicates that the drug has some in vivo fungistatic effect even at very low blood levels. Among those patients treated with intravenous amphotericin B, preliminary results were dramatic with clinical improvement and cultural conversion.

Progressive disseminated histoplasmosis: Two patients received oral amphotericin B and showed some clinical improvement, and negative cultures were obtained while the patients were under treatment. However, both patients relapsed within one month of discontinuing therapy. Two patients received intravenous amphotericin B but expired after only 3 infusions were administered. The remaining 2 patients experienced dramatic clinical improvement and conversion to negative cultures after therapy with intravenous amphotericin B.

The authors compared the treatment of histoplasmosis with amphotericin B at present to a similar stage in the treatment of tuberculosis in the early streptomycin era. They also pointed out that, although surgery had been of definite value in appropriate cases, fear of an organism resistant to therapy has been a major deterrent to this approach. The availability of a specific therapeutic agent will undoubtedly make this approach feasible.

Vogel and Crutcher[15] treated one case of disseminated histoplasmosis with meningeal involvement with intravenous amphotericin B in doses of 0.75 mg. per kilogram per day to 1.5 mg. per kilogram three times weekly for about 5 months with clinical improvement and reversion of the spinal fluid to cultural negativity.

Utz and his colleagues[13] treated 4 patients, 3 with disseminated histoplasmosis and one with histoplasmosis presumably localized to the chest, with amphotericin B orally. None showed any improvement and one patient expired. Two of these patients subsequently received amphotericin B intravenously. One was a 53-year-old white man with pulmonary and disseminated disease who received 60 to 80 mg. of amphotericin B intravenously daily for 90 days and showed marked clinical improvement and reversion to cultural negativity. The second case was an infant with far-advanced disseminated disease who expired after 5 days of treatment with amphotericin B orally and 15 days of treatment with amphotericin B intravenously.

The authors concluded that amphotericin B appears to have some usefulness in the treatment of histoplasmosis when given intravenously.

Aspergillosis.—Two patients with pulmonary aspergillosis, one with a draining thoracic sinus, have received amphotericin B intravenously. One child received amphotericin B intravenously for 3 months, followed by oral amphotericin B for 3 months, with clinical improvement and partial healing of the draining sinus. The second patient received therapy for only 15 days, with no improvement, at the end of which time the patient left the hospital.

Candidiasis.—One patient with *Candida parakrusei* infection of the eye following a corneal transplant received amphotericin B in a 5 to 10 per cent solution topically for 26 days, and amphotericin B intravenously for 7 days, with complete clearing of the infection. The graft, however, failed to take and the eye was subsequently enucleated.

Mycetoma.—A single case of far-advanced mycetoma (Madura foot) due to *Monosporium apiospermum* was treated for 20 days with intravenous amphotericin B with essentially no improvement.

Chromoblastomycosis.—Costello, DeFee, and Littman[16] have treated a single case of chromoblastomycosis due to *Hormodendrum pedrosoi* in a Negro man with injections of amphotericin B into the lesion. The patient received a series of 8 weekly or biweekly injections varying from 20 to 25 mg. of amphotericin B admixed with 2 per cent procaine. He received a total dosage of 245 mg. of amphotericin B, with complete clinical resolution of the lesion. The procaine-amphotericin B led to complete destruction of the parasite, prompt sloughing of the lesion, and eventual healing of the skin.

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DISCUSSION

At the outset it should be stressed that the evaluation of a fungicide on the course of systemic mycoses in man is made extremely difficult by many factors. The small number of patients available to the individual investigator makes it imperative to have a thorough understanding of the disease for proper interpretation of results. Although a great deal of information has been accumulated, much remains to be learned concerning the many facets of the natural course of the systemic mycoses. There is an easily understandable reluctance on the part of the clinician to withhold a potentially effective medication in order to form ideally matched control groups. The relatively few patients available for study make necessary the utilization of all case material to obtain a sufficient number in order to formulate an opinion. This requires in many instances a community-wide cooperative effort which, in turn, involves multiple observers. Unbiased observations are difficult, if not impossible, to obtain in such situations. Adequate follow-up periods must be measured in years before preliminary opinions can be substantiated. When dealing with humans the majority of these requirements cannot be met, and thus conflicting views and changing opinions are not only encountered but are to be expected. Realizing these shortcomings, we nonetheless feel that there is considerable practical value in presenting our clinical experience at this time.

Our findings to date, as well as those of other investigators, suggest that amphotericin B is worthy of further clinical evaluation in a wide variety of systemic mycoses including coccidioidomycosis, cryptococcosis, North American blastomycosis, histoplasmosis, candidiasis, chromoblastomycosis, and aspergillosis. Elucidation of its exact status as a therapeutic agent in any of these diseases still awaits further trial.

Our clinical experience with the use of amphotericin B has been primarily in the treatment of coccidioidomycosis. In some instances the drug when given

intravenously appeared definitely to influence favorably the course of this disease, so that the patient with progressive disseminated coccidioidomycosis shortly after the inception of treatment developed an improved feeling of well-being, increased appetite, weight gain, defervescence, healing of cutaneous, osseous, and pulmonary lesions, finally appearing clinically well. Even patients with meningeal involvement have in a few instances demonstrated similar striking improvement. This clinical response may be reflected in the laboratory findings, in that anemia is corrected, sedimentation rate decreases, complement fixation titer decreases, and negative skin tests have returned to positivity.

However, the laboratory response has not always paralleled in the expected manner the clinical course of the disease. This has been particularly true of the complement fixation test, which is considered of inestimable value from the standpoint of evaluating the status of the patient and prognosticating the future course. It was not possible in all instances to obtain complement fixation titers at frequent intervals; however, among those patients where this was possible one of several patterns was seen.

Three patients, who all clinically improved following treatment, showed essentially no change in the titer of their complement fixation tests for coccidioidomycosis. Two of these patients have remained clinically improved over a 4- and 5-month follow-up period, respectively, while the third patient, who had coccidioidal meningitis, relapsed 7 months after treatment.

Two patients showed decrease in their complement fixation titer for coccidioidomycosis. One of these patients 10 months after treatment remains clinically well. The other patient, with bony involvement, showed no clinical improvement despite the serologic improvement.

Finally, 4 patients showed significant increase in their complement fixation titer for coccidiodomycosis of two or more tube dilutions, in spite of marked clinical improvement. Of these patients, one relapsed 4 months after treatment, and the remaining 3 have maintained their improvement with no clinical evidence of active disease over follow-up periods of 3 to 11 months. The fact that persistently high complement fixation titers remain in several patients who otherwise show apparent clinical remission requires cautious interpretation and further detailed follow-up studies before definite opinions can be formulated.

Our tentative opinion to date is that amphotericin B in some instances definitely influences favorably the course of coccidioidomycosis in man. None of our patients has been followed for a sufficient period of time to allow final judgment as to its ultimate value.

Finally it should be stressed that the use of amphotericin B supplements but does not supplant those supportive measures heretofore recommended. These include: bed rest; a high-protein, high-vitamin, high-caloric diet; excellent nursing care; and drainage of subcutaneous abscesses and other surgical procedures where indicated.

Amphotericin B appears to be the most promising agent currently available for the treatment of cryptococcosis, histoplasmosis, and North American blastomycosis. Here again the administration of amphotericin B appears clinically to influence favorably the course of these diseases in certain patients. As in

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coccidioidomycosis, final evaluation of amphotericin B awaits further long-term follow-up.

It is reasonably well established that amphotericin B is poorly absorbed from the gastrointestinal tract and that the drug given by this route in the majority of instances failed to influence appreciably the clinical course of any of the systemic mycoses, even in large doses over long periods of time. However, Fiese,[17] Klapper, Smith, and Conant,[22] Lehan and associates,[24] and Utz and colleagues[13] each report in detail one patient showing clinical improvement with the oral administration of amphotericin B. This tends to support the concept that under certain circumstances sufficient drug is absorbed in some individuals to influence the course of the disease. At present, therefore, in those instances where intravenous therapy is not possible, intensive oral therapy with amphotericin B may be given an adequate trial. The drug is well tolerated orally in doses ranging from 8 to 12 Gm. per day, and in one patient in doses as high as 16 Gm. per day in our experience. In some instances, however, transitory nausea, anorexia, and diarrhea have been reported with amphotericin B orally in doses of 5 Gm. per day.[13]

Other routes of administration of amphotericin B have been employed, and in special situations may be of value.

The intravenous route appears to be the most satisfactory method of administering amphotericin B at present. In our experience as well as that of other investigators the optimal dosage of amphotericin B for intravenous use in the adult is in the range of 0.7 to 1.4 mg. per kilogram (50 to 100 mg.) per day. Evidence is accumulating which indicates that the drug is better tolerated and equally effective in the same dosage level when administered on alternate days.

TOXICITY

It must be stressed that the initial dose should be in the range of 5 to 10 mg. per day, with increments of 5 to 10 mg. depending upon the reaction of the patient. Some patients initially will develop fever and shaking chills, anorexia, nausea, vomiting, chest pain, anxiety, and headache. Under such circumstances the drug should be discontinued until the following day. In general, the reactions appear to be less with subsequent infusions. In a large number of our patients a slow increase in blood urea nitrogen has been noted upon continued administration of the drug. However, temporary discontinuation of the drug has uniformly been followed by a return of the blood urea nitrogen to the pretreatment range. In one instance the drug was continued despite a rising blood urea nitrogen, and the blood urea nitrogen returned to the normal range on continuous treatment. It is recommended, nevertheless, that in the face of a rising blood urea nitrogen the drug be discontinued until the blood urea nitrogen returns to normal. The drug should be readministered beginning again at a lower dosage level and increasing the drug gradually over a longer period of time.

In 3 of our patients we have noted a persistent drop in the hematocrit ranging from 6 to 12 units. It is recommended that appropriate hematologic, liver function, and renal function studies be done periodically on all patients on prolonged therapy with amphotericin B.

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An annoying complication is the development of phlebitis at the site of infusion, and it is therefore important if a prolonged course of amphotericin B is contemplated to utilize the most distal veins first, using a small needle and a slow rate of infusion. In one instance it became necessary, in order to continue the administration of the drug, to employ an indwelling polyethylene catheter inserted into the inferior vena cava via the femoral vein. It should be reemphasized that the drug is administered over a 6- to 8-hour period. In one instance in which it was inadvertently infused rapidly[12] (28 mg. in 40 minutes), the patient developed grand mal convulsions, ventricular fibrillation, and cardiac arrest, which fortunately responded to a sharp blow on the chest.

Other manifestations of toxicity reported in the literature include: transitory vestibular disturbances, flushing, sweating, fatigue, drowsiness,[20] hypokalemia in one patient,[12] generalized pain,[12] and weight loss.[21] All manifestations of toxicity have to date been reversible upon discontinuation of therapy. One instance of possible hepatic toxicity has been reported.[26]

Preliminary studies directed toward establishing the pathogenesis of the rising blood urea nitrogen often seen with amphotericin B therapy have shown an associated decreased rate of glomerular filtration and a decreased renal plasma flow.

Laboratory evidence[31,32] suggests that resistance to amphotericin B is a distinct possibility. Such a phenomenon has not been observed to date at a clinical level.

CONCLUSION

1. Amphotericin B is a new polyene antifungal antibiotic with the tentative empirical formula of $C_{46}H_{73}NO_{20}$.

2. In vitro amphotericin B inhibits a wide variety of pathogenic and nonpathogenic fungi including: *Blastomyces dermatitidis*, *Candida albicans*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Coccidioides immitis*.

3. Amphotericin B has favorably influenced the course of experimental infections with *Candida albicans*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Coccidioides immitis*.

4. Amphotericin B appears to be poorly absorbed from the gastrointestinal tract, and the intravenous route appears to be the most effective means of administering amphotericin B at present.

5. We have treated 22 patients with deep mycoses including coccidioidomycosis, cryptococcosis, North American blastomycosis, *Candida parakrusei* infection of the eye, aspergillosis, and mycetoma with amphotericin B intravenously in dosages of 0.7 to 1.4 mg. per kilogram daily or on alternate days over periods of 2 weeks to 4 months.

6. From our experience as well as that gathered from the literature, amphotericin B appears to be of significant value in the treatment of the systemic mycoses including coccidioidomycosis, cryptococcosis, North American blastomycosis and more recently South American blastomycosis,[34] histoplasmosis, aspergillosis, sporotrichosis, and chromoblastomycosis, and warrants further detailed study and clinical trial.

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7. The most common manifestations of toxicity have included: anorexia, nausea, vomiting, anxiety, chest pain, rising blood urea nitrogen, and fall in hematocrit. All manifestations have disappeared upon temporary cessation of therapy.

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RECENT ADVANCES IN AND RESULTS OF SURGICAL TREATMENT OF PULMONARY TUBERCULOSIS

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THERE has been relatively little change in the concept of the application of surgical procedures in the treatment of pulmonary tuberculosis during the past 5 years. This is in sharp contrast to revolutionary changes that occurred in this type of therapy during the preceding 5-year period. The most important recent advance has come from a better knowledge through follow-up studies of the eventual fate of patients treated with chemotherapy. This has resulted in a better definition of indications for, and a more exact timing of, the application of surgical treatment. It seems worth while to review briefly the history of the development of the surgical therapy for pulmonary tuberculosis and to point out the factors that have brought about the measure of agreement that now exists. Areas in which honest differences of opinion still remain will be discussed. Also an attempt will be made to indicate the information that we must have to resolve some of the controversies that still exist in the application of the surgical procedures now commonly used in the treatment of pulmonary tuberculosis.

The surgery of pulmonary tuberculosis had its origin shortly after the beginning of this century with the development of surgical techniques that later were designated as "collapse therapy." First came extrapleural thoracoplasty. Then followed intrapleural pneumothorax with its corollary operation, intrapleural pneumonolysis. Still later came diaphragmatic paralysis—both permanent and temporary—intercostal neurectomy, scalenotomy, and extrapleural collapse—with and without plombage, pneumoperitoneum, and cavernostomy. The technique of thoracoplasty underwent many modifications, and concepts as to its indications were legion. Collapse measures were applied on a trial basis going in serial fashion from procedures of lesser magnitude to those more hazardous and lasting in their effects. Serious complications resulting in death or severe loss of respiratory function were accepted by both physician and patient because of the high mortality incident to the disease under attack. In spite of these risks application of collapse therapy resulted in a lower mortality from the disease and a higher percentage of patients achieving an inactive status than with bed rest alone. Chaos in the surgical therapy of pulmonary tuberculosis reached its peak about the time of World War II. Order has gradually been restored since that time by (1) the discovery of effective antituberculous drugs,

(2) the development of the Pembine-type conferences, and (3) the chemotherapy conferences which rapidly disseminated knowledge gained from controlled cooperative studies.

CHEMOTHERAPY

The scope of this paper does not permit a discussion of the various drugs that have been found useful in the treatment of pulmonary tuberculosis. Drug therapy which has now become the basic treatment in this disease will be referred to in this paper as chemotherapy. The advent of chemotherapy with its proved effectiveness in quickly controlling the acute toxic manifestations of the infection soon rendered obsolete collapse measures, such as pneumothorax, phrenic nerve interruption, and pneumoperitoneum, although the latter procedure still has its advocates. Tuberculous tracheobronchitis responded well to chemotherapy and thus was no longer the feared complication that menaced the patient and rendered hazardous the application of surgical therapy. It was quickly learned that with adequate coverage with chemotherapy and with the improvements in the technique of pulmonary resection this procedure could be applied in the treatment of pulmonary tuberculosis with little risk of the feared complications of spread of the disease and a mixed infected empyema due to a bronchopleural fistula. By 1950 pulmonary resection challenged thoracoplasty as the operation of choice in treating advanced cavitary disease and has now largely replaced it in the majority of clinics.

PEMBINE-TYPE CONFERENCES

In 1944 a conference was held in Pembine, Wisconsin, attended by physicians from Michigan, Minnesota, and Wisconsin who were interested in the treatment of pulmonary tuberculosis. It was called a tuberculosis treatment conference. The concept of such a conference where differences of ideas concerning the treatment of tuberculosis would be aired by reviewing the case histories of unselected series of patients was born in the minds of three physicians who had conducted a survey of treatment of patients in several county sanitoria. They were struck by the wide variance in the application of collapse therapy measures and felt that with unbiased review of these measures in yearly conferences some orderly rationale would replace the chaotic situation. Conferences of the Pembine type are now held yearly in all parts of the country. Credit must be given to the Tuberculosis Division of the Veterans Administration for stimulating and guiding the development of these conferences. They are eagerly attended. They have been of great value in the rapid dissemination of knowledge of current developments and in bringing about a measure of agreement among physicians in the application of therapy in pulmonary tuberculosis.

VETERANS ADMINISTRATION ARMED FORCES CONFERENCES ON THE CHEMOTHERAPY OF TUBERCULOSIS

Chemotherapy of tuberculosis is a development of the past decade. The development of these antituberculosis drugs gave the physician for the first time

a potent weapon capable of modifying the course of the infection. With their discovery, problems of dosage, toxicity, development of bacterial resistance, and length of administration immediately arose. The Tuberculosis Division of the Veterans Administration in order to solve these problems in the shortest possible period of time set up cooperative studies in the hospitals under their control. They were joined in this effort by Armed Forces Hospitals and certain other institutions who cared to cooperate. Reports of these studies were presented to "Chemotherapy Conferences." Rapid developments in changing concepts and in the discovery of new drugs necessitated, at first, two conferences a year. Now they are held annually. Eighteen such conferences have been held in which physicians report the results of studies relating to all phases of antituberculous chemotherapy. Interpretation of data from these cooperative studies based on sound experience gives access to more data, shortens time necessary to gain information, and points the way to future studies. These conferences have prevented in the application of chemotherapy the chaotic situation that developed in the collapse therapy era in the treatment of tuberculosis.

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CHANGING CONCEPTS IN THE AIM OF THERAPY

The aim of therapy in pulmonary tuberculosis must consider not only the health and welfare of the patient but also that of the community if this contagious disease is to be finally eradicated. Before the collapse therapy era it was considered sufficient if the patient could temporarily get the pulmonary infection under control and learn to live with the disease. The prevailing concept of the aim of therapy was prolongation of life with little thought of cure or of protection to others. During the collapse therapy era the goal was to arrest the disease, render the patient noninfectious, and to some extent protect against further relapse. Great stress was placed upon closure of cavities and the obtaining of a negative sputum in addition to control of symptoms and extension of the infection. Sputum studies, however, rarely included cultures of sputum and examination of gastric washings was seldom done. Patients were examined by routine radiographic techniques which rarely included lateral projections. Planographic techniques had not yet been developed for the more accurate delineation of cavities.

At present criteria for the attainment of an acceptable end result have become more exacting. The sputum and gastric washings must repeatedly be negative to culture. There must be no cavities remaining as determined by x-ray techniques including planograms. The roentgenograms of the chest must show no change over a period of 3 months. The patient who following treatment can pass these tests is said to have reached the "target point." This may not be the end of the period of treatment. Concern for the future health of the patient may make advisable resectional surgery and/or continued chemotherapy. Thus surgery and chemotherapy in the treatment of pulmonary tuberculosis are used not only to bring the infection under control but to prevent future exacerbation of the disease.

SURGICAL PROCEDURES

Resection and thoracoplasty remain the chief surgical procedures in the surgical therapy of pulmonary tuberculosis. Phrenic nerve interruption no longer is used as a primary therapeutic procedure but may be occasionally employed as an adjunct to resection to aid with "space-filling" problems. Discontinuation of pneumothorax therapy has eliminated the indication for closed intrapleural pneumonolysis. Extrapleural pneumothrax has been replaced by thoracoplasties of the extraperiostial type with plombage. The backlog of unexpanded lungs from the pneumothorax era has almost been eliminated so that fewer indications are found for decortication. Cavernostomy as a salvage procedure is still used in some clinics in treating poor-risk patients with cavities either too large or so located that resection and thoracoplasty are not feasible.

TECHNIQUE

The technique of pulmonary resection has become fairly well standardized. Careful dissection, avoiding breaking into areas of active disease, meticulous closure and covering of the bronchial stump, exact hemostasis especially in securing the hilar vessels, and adequate drainage of the pleura postoperatively are important in achieving low mortality and morbidity rates. Wedge resections employing crushing clamps on the lung should be reserved for small subpleural lesions. Segmental resections should be accomplished by dividing the arteries and bronchus to the diseased segment leaving the veins to be secured as the segmental plane is developed to avoid depriving remaining segments of their venous drainage. Reconstitution of the lung by apposing the raw surface of the remaining segments against the surface of the neighboring lobe with sutures of fine material along the visceral pleural edge will aid in sealing off small surface leaks that might be troublesome in delaying re-expansion of the lung. A concomitant thoracoplasty should not be necessary unless a segment in addition to a major lobe has been removed. A preresection thoracoplasty performed 4 to 6 weeks prior to an extensive resection is a useful adjunct to minimize the space-filling problem. Preservation of the first rib and transverse processes and removal of shorter lengths of the ribs reduces the resultant deformity. This same type of thoracoplasty is employed to collapse persistant air pockets and apical empyemas that may complicate resections. Fewer thorcoplasties are being performed in conjunction with resections since it has been learned that the danger of reactivation of residual disease in overdistended segments is not as great as was formerly feared.

The technique of extrapleural thoracoplasty designed as a definitive operation is rapidly becoming a lost art. Many surgeons now completing their training in thoracic surgery have never seen this type of thoracoplasty performed. It should include removal of all of the first and second ribs and graded lengths of additional ribs to secure the desired collapse. Transverse processes starting with the third process to below the level of the cavitary area should be removed. The first, second, and third intercostal muscle bundles with their vessels and nerves should be severed posteriorly to allow an apicolysis, dropping the dome of the

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parietal pleura to the level of the fourth posterior rib. This operation is performed in stages easily tolerated by the patient at 2-week intervals.

Many surgeons (myself not included) prefer an extraperiosteal thoracoplasty using a space-filling plomb. Plastic spheres, paraffin, and Ivalon sponge are the space-filling materials now commonly used. The plastic spheres are usually enclosed in a polyethylene bag to prevent migration. The procedure is a one-stage operation except when as part of the planned procedure the spheres are removed at a later date along with the denuded ribs. Careful attention must be paid to developing the gutter of the chest by cutting the intercostal muscles in order to gain cavity closure.

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TIMING OF SURGERY

It is impossible to define the indications for surgery without a consideration of the factor of time. Adequate coverage with effective drugs is important in reducing the complication rate especially following resection. Bacterial resistance to all of the effective drugs develops with long-term chemotherapy. Interruption of drug therapy increases the probability of the development of drug resistance. Ideally, resection, when indicated, should be carried out in original treatment cases between the fourth and the eighth month of therapy. Raleigh and Steele[1] in summarizing the results of cooperative studies following the sixteenth chemotherapy conference (1957) stated that "continued expectant treatment using the same chemotherapeutic regimen beyond this point (8 months) in the face of persistent cavity is less likely to yield a delayed success than to result in disappointment, loss of the patient's time, and, at least in some cases, in the loss of ground already gained due to x-ray worsening and bacteriologic escape or relapse. If, for any reason, surgical treatment is not possible, chemotherapy should be prolonged greatly and perhaps indefinitely." In re-treatment cases 2 to 3 months of preoperative chemotherapy is sufficient for protection during the time of surgery. Surgery thus becomes a part of the original plan of therapy in a significant number of patients and is not reserved for so-called "medical failures."

INDICATIONS FOR RESECTIONS

Changing indications for resection represents the major development during the past 5 years in the surgical treatment of pulmonary tuberculosis. The ability of chemotherapy to modify the usual course of this infection was at first not fully realized. Time had to elapse before painstaking pathologic and bacteriologic studies yielded information concerning the significance of residual lesions following long-term chemotherapy. It was soon recognized that new follow-up studies had to be undertaken since the prognosis of the disease following chemotherapy appeared different from that following rest and collapse therapy.

FACTORS INFLUENCING SURGICAL INDICATIONS

A concept combining an estimate of the pathologic nature of the lesion from the radiographic shadow that it casts with the status of the presence or absence of tubercle bacilli in the sputum is useful in the discussion of indications for

surgery. These two factors which indicate the presence or absence of continuing activity of the disease are most significant in determining prognosis. Obviously other factors, such as age of the patient, pulmonary function, and other diseases of grave prognosis, must be considered before recommending that surgery is indicated in any particular patient. Whether or not the tubercle bacilli are resistant to the major drugs (streptomycin and isonicotinic acid hydrozide—INH) may influence the surgical decision especially as to the type of surgery indicated.

SURGICAL INDICATIONS IN CLOSED NEGATIVE LESIONS

Closed negative lesions are residuals represented by linear scarring or nodules remaining in patients having a persistently negative sputum on culture. They represent morphologic evidence of disease. It is known that nodules resected following 6 to 8 months of chemotherapy may contain tubercle bacilli that by culture techniques can be proved viable. Theoretically these nodules represent a threat to the patient's future health. The practical problem, however, is whether removal of these residuals alters the prognosis to a degree that justifies major surgery. Raleigh[2] has studied the prognosis of 227 patients in the closed negative category. The relapse rate at the end of 4 years was 16 per cent for those patients whose lesions had been resected and 19 per cent for the nonsurgical group. Although the quality of the relapses was somewhat more severe in the nonsurgical group, there were no deaths in either group. This small percentage difference in relapse does not justify subjecting as a group these patients to pulmonary resection.

There are several types of lesions within the closed negative category that vary in prognostic significance. Calcified lesions, regardless of size, nodules remaining as a residual following tuberculous pneumonia, nodules in the anterior segments, and linear fibrotic lesions do not tend to reactivate. However, nodules that represent filled in cavities and recurrent or "browsing" nodules (new nodules appearing near older ones in the same or neighboring segment) in young individuals with adequate pulmonary function should be resected.

SURGICAL INDICATIONS FOR OPEN NEGATIVE LESIONS

Cavities may remain open following 6 to 8 months of chemotherapy in patients whose sputum quickly converted to negative. The residual cavities may be true tuberculous cavities with walls containing epithelioid cells and having a caseous lining. In these cavities tubercle bacilli can usually be found, but they may or may not grow on culture media or produce tuberculosis when inoculated into experimental animals. Certain cavities in this category are bullae, bronchiectatic cavities, or cysts. Thin-walled cysts more commonly remain as residuals of obvious tuberculous cavities since the advent of INH. They are often referred to as "isoniazid cysts." The walls of these air-filled cysts are composed of fibrous tissue without a true epithelial lining. In some cysts small rests of tuberculous granulation tissue can be recognized, but in others there remains no clue that the cyst once was a tuberculous cavity.

Again Raleigh[2] has given information concerning the prognosis of the patient who has an open lesion and has had a negative sputum for 6 months following

adequate chemotherapy. The relapse rate was 50 per cent in 2.5 years in the nonsurgical group. The mortality in this group due to tuberculosis was 7.5 per cent. The relapse rate at 2.5 years was only 15.5 per cent, and there were no deaths due to tuberculosis in the patients who had their open lesions resected. This is clear-cut evidence that resection should be considered in patients having open negative lesions.

Individualization is important in determining the patients who should have resection for open negative lesions. As a category it is made up of a variety of lesions all of which do not have the same tendency to relapse. The thick-walled cavities that obviously contain caseous material should be resected. Bullae, bronchiectatic cavities, and "isoniazid cysts," when located in upper lobes, may not cause relapse in a significant percentage of patients. Cystic residuals in lower lobes are more likely to cause symptoms and should be resected. Length of time of negativity becomes an important factor in evaluating the risk of an open negative lesion since follow-up studies indicate that the longer the sputum remains negative in conjunction with an open cavity the less likelihood there is of relapse. Studies are still required that will lead to a better recognition of the types of lesions in this category and a more accurate assessment of the threat they present to the patient.

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PROGNOSIS FOR PATIENTS WITH OPEN POSITIVE LESIONS

Patients who have open cavities and a positive sputum at the observation point of 6 to 8 months of chemotherapy are in a precarious situation. Raleigh,[2] in following 40 patients in this category, reports that 17 died of tuberculosis (42.5 per cent), 12 still had active disease, and 11 became inactive (9 following thoracoplasty). Twenty-four of 30 patients who had resection of their cavities attained an inactive state. One patient died following resection and 5 remained active. There was one bacteriologic relapse in the 24 patients who had resection. Due to the poor prognosis, patients having open positive lesions should have surgical resection or closure of the cavities by thoracoplasty if there are no compelling contraindications to surgery.

RESECTION FOR OPEN POSITIVE LESIONS

Resection is the procedure of choice in patients having open positive lesions if the cavities are limited to one lobe of the lung. Bilateral cavitation does not contraindicate resection if pulmonary function is adequate and the cavitary areas are limited in extent. The hazards of pulmonary resection increase with the extent of the resection. The presence of active tuberculous bronchitis and the emergence of tubercle bacilli resistant to the two major drugs (i.e., streptomycin and INH) increase the risk of bronchopleural fistula and empyema as complications following resection.

MORTALITY AND COMPLICATIONS OF RESECTION

Reports are available from the Veterans Administration Armed Forces Cooperative Studies[3] of 6,290 pulmonary resections performed for tuberculosis

between July 1, 1952, and June 30, 1957. Since this report combines the results of a large number of surgeons it is probably representative of the results that can be expected in the average institution although undoubtedly some surgeons may have achieved lower mortality and complication rates.

There were 41 (12.0 per cent) surgical deaths in 330 pneumonectomies. Lobectomy had a surgical mortality of 2.7 per cent (65 deaths in 2,362 patients). Segmental resection carried a risk of only 0.9 per cent (26 deaths in 2,775 patients). There was no mortality in 794 patients having subsegmental resections. The corresponding mortality rates for the final year of the report (July, 1956, through June 30, 1957) were 5.7 per cent for pneumonectomy, 2.1 per cent for lobectomy, and 0.57 per cent for segmental resections.

Spread of the infection following resection, once a frequent and dreaded complication, now occurs in less than 1 per cent of patients.

Bronchopleural fistula and empyema remain the major complications causing prolonged morbidity following resection. In the 6,290 patients this complication occurred following pneumonectomy in 16 per cent, lobectomy in 4.0 per cent, segmental resection in 3.8 per cent, and subsegmental resection in 1.0 per cent. This complication was more frequent in resections performed on re-treatment cases and on patients with persistently positive sputums. This reflects the importance of adequate drug coverage for patients having resections and emphasizes the advisability of performing a resection in the 4- to 6-month period of chemotherapy on a patient in whom the indication for eventual resection is obvious.

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LATE RESULTS FOLLOWING RESECTION

Late deaths from tuberculosis occur in about 10 per cent of patients having pneumonectomy and 4 per cent of all patients having resections. Of the remaining patients approximately 90 per cent will obtain a good result and remain healthy under conditions of normal activity. Ten per cent will still have active disease requiring continuing treatment.

THORACOPLASTY FOR OPEN POSITIVE LESIONS

Thoracoplasty as a surgical procedure is complementary to resection and actually competes with it in only a very narrow band of the spectrum of tuberculous lesions indicating surgery. Thoracoplasty should be considered (1) when resection would require a total pneumonectomy, (2) when resistant organisms are present, (3) when active tuberculous bronchitis is present, and (4) when poor pulmonary function renders resection unduly hazardous. Closure of cavities and conversion of sputum can be expected in 50 per cent of patients following thoracoplasty. Resection as a definitive procedure becomes feasible in a significant percentage of so-called thoracoplasty failures. Significant clinical improvement and prolongation of life may be attained even in those patients who fail to reach an inactive status. The surgical mortality for thoracoplasty in this salvage group of patients is 1 per cent.

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PLOMBAGE TYPE OF THORACOPLASTY

Extrafascial and extraperiosteal plombage is (in my opinion) a third-rate operation as compared to the standard extrapleural thoracoplasty. It is recognized that this procedure, now high in the favor of many thoracic surgeons, has many advantages. The advantages set forth are (1) one operation, (2) no deformity, and (3) better conservation of pulmonary function. The overwhelming disadvantage, however, is the risk inherent to introducing a mass of foreign material into a created body cavity close to infected tissue. Macarthur[4] in a current article states, "Patients with a plombage are always at risk and the possibility of a latent space infection should be in the mind of those responsible for their after-care." Walkup[5] who has given up this operation reports that early and late space infections occurred in 15 per cent of his patients treated with a Lucite ball plombage. This complication is a major one that requires removal of the plomb, unroofing of the created cavity, and prolonged drainage of the infected space. The results of this procedure in cavity closure and sputum conversion should not be compared with the results of extrapleural thoracoplasty which is generally used over larger cavities and more extensively destroyed lungs. A 1 per cent mortality and 80 to 90 per cent cavity closure and sputum conversion are reported by the advocates of this surgical procedure. Extraperiosteal plombage seems to find its best application when used over small apical cavities in patients whose pulmonary function is poor.

CAVERNOSTOMY

Cavernostomy is useful in a limited number of patients as a salvage procedure. Chemotherapy has almost completely eliminated the complications that formerly attended drainage of a tuberculous pulmonary cavity. Cavernostomy should be considered in patients with extensive disease not suitable for other forms of surgical therapy when there is (1) a cavity under thoracoplasty collapse, (2) a cavity in the superior segment of a lower lobe, or (3) a large cavity in the upper lobe. Occasionally following cavernostomy a more definitive procedure such as resection may become feasible. In other patients sputum conversion may permit patients to return to their homes even though they must accept as a price a permanent bronchocutaneous fistula.

SUMMARY

The surgical treatment of pulmonary tuberculosis has undergone no important changes in the past 5 years. The agreement that now generally exists as to the treatment of pulmonary tuberculosis has resulted from (1) the advent of chemotherapy which rendered temporary collapse therapy unnecessary, (2) Pembine-type conferences which rapidly disseminated knowledge of current developments, and (3) the Veterans Administration Armed Forces cooperative studies which saved valuable time in obtaining information concerning the proper use of chemotherapy in tuberculosis. Resection and thoracoplasty collapse remain the principal surgical measures of proved value in removing and closing

the remaining cavities following an adequate course of chemotherapy. The risks of these procedures are justified by the poor prognosis of the patient with a positive sputum and open cavities. Certain patients who have achieved a negative sputum but who have residual disease known to cause relapse frequently should have resections in an attempt to safeguard their future health. Resection is the surgical procedure of choice for patients having segmental or lobar disease when adequate drug coverage is still available. Thoracoplasty competes with resection when total pneumonectomy must be considered and when there is bacterial resistance to the major drugs. Cavernostomy is useful as a salvage procedure to obtain a negative sputum when other surgical measures are not feasible. The aim of surgical therapy should not be to fit the patient to a certain preferred surgical procedure but to select the surgical therapy best adapted to the problem presented by the patient.

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Cancer

ON THE ESTIMATION OF THE INCUBATION PERIOD IN MALIGNANT DISEASE

The Brief Exposure Case, Leukemia

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NO DESCRIPTION of an infectious disease would be considered complete without a statement of the incubation period. Although a systematic collection of data has been presented by Kennaway,[11] it is safe to say that on the whole little attention has been given to this aspect of malignant disease. It is our intention in this series of papers to discuss methodologic problems in this area.

Since there is much confusion in terminology, definitions of two terms are necessary. The first is appearance time of disease, which is the time from some specified event, as first exposure, to the appearance of the disease. The second term, incubation period, was developed for infectious diseases and is usually used to denote the period of multiplication of the invader from the time of receipt of infection to the time of development of the symptoms of illness.[10] In these presentations, the concept of incubation period is extended to include the period of multiplication of an invading strain of abnormal host cells. The end of the appearance time or the incubation period will be taken to be the time of diagnosis unless otherwise specified. When the exposure is brief, these two periods can be considered as the same. However, when exposure is prolonged or continuous, the incubation period is almost always less than the appearance time after first exposure.

In this first presentation we will consider the estimation of the incubation period of a malignant disease in which a single brief exposure is sufficient to produce the disease. For illustrative purposes, leukemia has been selected.

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It has been recognized by many authors that radiation can contribute to the genesis of this disease.[1,3,5,12,13,16-21] At present, however, there seems to be no particular reason to believe that radiation is the only cause of leukemia. In the detection of other causes of leukemia, it is helpful to have some idea of what period in the patient's life should be searched. To this end, we have examined the available data on the incubation period of leukemia. Such data have been found, in sufficient quantity to warrant analysis, in three general areas: the studies of the Atomic Bomb Casualty Commission in Hiroshima, the studies of x-ray treatment of spondylitis, and the experience of early life. In each case a reasonable estimate of the time of the generating event is available.

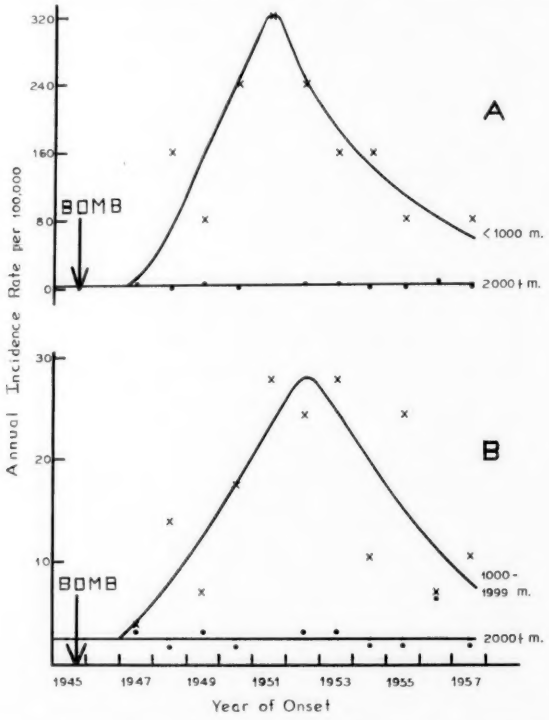

Fig. 1.—The annual incidence of leukemia following the atomic bomb explosion among survivors who were residents of Hiroshima city at the time of diagnosis. *A*, Persons less than 1,000 meters from the hypocenter compared with persons 2,000 or more meters from the hypocenter at the time of the explosion. *B*, Persons 1,000 to 1,999 meters from the hypocenter compared with persons 2,000 or more meters from the hypocenter at the time of the explosion. Note the difference in scale between *A* and *B*. In *A* there is about a hundred-fold increase in rate while in *B* there is only about a tenfold increase in rate.

In Fig. 1 is presented a reanalysis of the Hiroshima data of Wald.[21] This clearly suggests that the peak incidence of leukemia in this population occurred in 1951 or 1952, that is, about 6 years after the radiation exposure in August, 1945. It is probable that there is a greater underestimate of the number of cases with onset before 1950 than after because the investigations were not so intensively pursued in the earlier years. It is also conceivable that the data

for 1957 are not yet complete. It is our opinion, however, that the deficiencies in this information tend to give a slightly high estimate of the incubation period.

More detailed analysis of these data does not suggest that there are important differences in incubation period by dose, by age, or by type of leukemia. Of course, it should be noted that the numbers are too small and the dosimetry data too incomplete to state that such differences do not exist. The emphasis must be on the fact that striking differences have not yet been found. Further research in this area is in progress.

The second source of information on this subject is the excellent monograph of Court-Brown and Doll, *Leukemia and Aplastic Anaemia in Patients Irradiated for Ankylosing Spondylitis*.[3] Here the interval between a single treatment and diagnosis is reported for 10 persons and the conclusion is reached that the bulk of the cases of leukemia occur between 3 and 5 years after exposure.

There are two difficulties with this estimate. In the first place, the numbers are obviously very small. In the second place, the material was collected in such a way as to increase the relative probability of persons with a short incubation period being included in the sample. This second difficulty we are forced to accept for the time being and recognize that it will lead to an underestimate of the true incubation period for leukemia. Dr. Court-Brown has informed us that this material will be reviewed in the near future and should then provide data that are more appropriate for this purpose.

We have been reasonably successful, on the other hand, in our attempt to enlarge the available number of cases for analysis. This has been accomplished by including a few from other sources[7,17] and by taking the cases for whom dates of multiple exposure and date of diagnosis are given and defining the incubation period as the time from the center of the exposures to diagnosis. For this purpose, the central point of the exposure period was determined on a weighted basis so that the size of a given dose influenced the position of the estimated center in proportion to its size. In Fig. 2 is presented the distribution of these cases. It can be seen immediately that more than 90 per cent of the cases occurred within 9 years of exposure. In addition, the peak of the curve appears to come slightly earlier than in the Hiroshima experience, being about 4 years after exposure.

It is evident that making this estimate of the midpoint of exposure may bias the results when the interval between first and last treatment approaches twice the incubation period. In Table I can be seen evidence that this material is not seriously biased in this way. The possibility of excluding the cases with very long treatment periods was considered, but finally it was felt that inclusion probably gave a better picture of the true situation since there is another known bias that reduces the likelihood of inclusion of cases with long incubation periods.

Another source of concern is the appearance of cases very shortly after exposure. Specifically, there seems to be somewhat of an excess of cases in the first year after exposure. This is accentuated by the fact that one of the 5 cases that van Swaay[20] presents developed less than 12 months after the midpoint of the radiation exposure, although the rest of his cases seem roughly to fit the distribution presented here. This would give us 4 cases under a year or 5 within

15 months of the midpoint of treatment, which seems a little out of proportion. By contrast, the known rates for those exposed in Hiroshima do not start until 1947, at least 15 months after the atomic bomb was dropped.

Again such examination as was possible by age and dose did not suggest that these factors had any important influence on the length of the incubation period.

TABLE I. THE EFFECT OF LENGTH OF EXPOSURE ON THE ESTIMATE OF THE INCUBATION PERIOD OF LEUKEMIA AMONG PATIENTS IRRADIATED FOR ANKYLOSING SPONDYLITIS

LENGTH OF EXPOSURE	NUMBER OF CASES	MEDIAN INCUBATION PERIOD IN MONTHS
Single course	13	44
Less than 5 years	23	42
5 to 8 years	12	55
More than 8 years	3	106

Data of Court-Brown and Doll; Graham; and Silberberg, Frohman, and Duff.

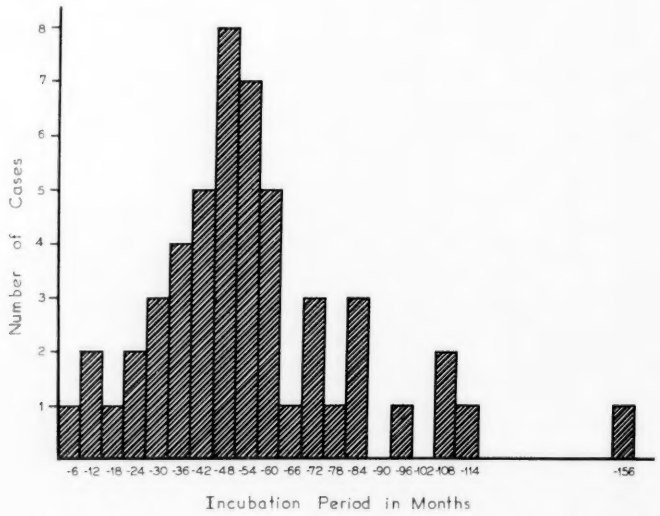

Fig. 2.—The distribution of incubation periods of leukemia cases following irradiation for ankylosing spondylitis. (Forty-one cases from Court-Brown and Doll;[3] 5 cases from Graham;[7] 5 cases from Silberberg, Frohman, and Duff.[17])

The third source is the mortality data in early life[14] which is presented in Fig. 3. Here again we have a similar distribution of appearance times with a peak in the fourth year of life and approximately 90 per cent of the cases occurring between 1 and 9 years of age. Again we are working with the same general type of curve. Incidentally, it is interesting to note that in some years the peak of the distribution shifts to an older age. For example, in the year 1956, the peak is in the fifth year of life.

That the distribution is the same for boys and girls even though the incidence is lower in girls is demonstrated by Fig. 4 which is prepared from data presented by Cooke.[2] It is of interest that the peak she found comes a few months earlier than the peak of the mortality curve presented in Fig. 3. The difference is presumably an indication of the life expectancy of childhood leukemia cases.

Fig. 3.—Leukemia death rates per 100,000 persons of specified ages for the years 1910, 1930, and 1950, U. S. A. death registration states. (Population figures adjusted for underregistration of births, except those of 1910.)

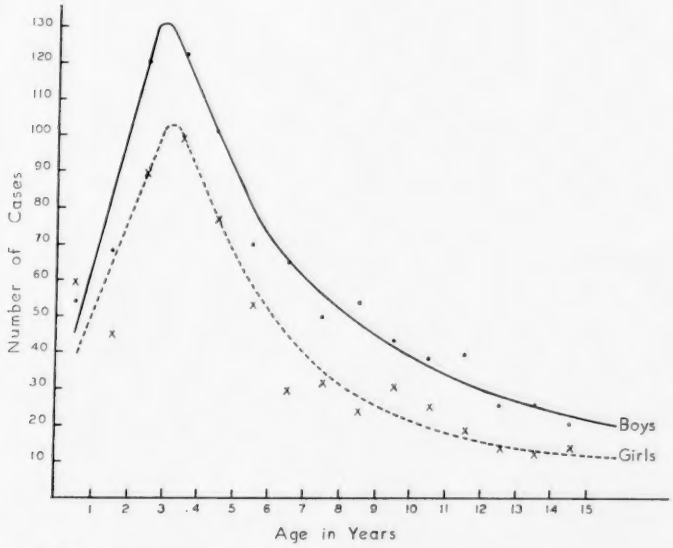

Fig. 4.—The appearance time distribution of leukemia in childhood, boys and girls compared, from data of Cooke.[2]

DISCUSSION

Three sets of data have been examined. From these we get several estimates of the incubation period of leukemia. The longest of these is derived from the Hiroshima experience. However, we have reason to believe that this is biased

toward the long side by an underestimate of the number of cases which actually occurred prior to 1950. On the other hand, the estimate from the spondylitis cases is probably biased toward an underestimate because the method of data collection would tend to underestimate the number of cases occurring many years after treatment. Admitting these two biases in opposite directions, it seems reasonable to put the material together and make a guess that the modal incubation time for radiation-induced leukemia in adults is approximately 5 years and that roughly 90 per cent of the cases will occur within approximately 10 years after exposure. This is in reasonable agreement with the statement of Langendorff[12] that the latent period is about 6 years. Unfortunately Langendorff does not tell us how he arrived at this conclusion.

The data relating to leukemia in childhood is on a somewhat less sound footing, for making an estimate of incubation time when we do not have a definite statement of the time and nature of the generating event is clearly risky. However, the distribution curves presented are sufficiently similar to those discussed above to warrant mention. It does not seem surprising that the incubation time suggested by these distribution curves should turn out to be somewhat shorter, for cell multiplication goes on at a higher rate in young individuals, and presumably a child weighing 20 to 40 pounds would develop symptoms with fewer leukemic cells in its body than would an adult.

If we examine the question as to whether this peak of childhood leukemia is really radiation-induced as in the other two instances, it must be admitted that the evidence is scant. However, it seems possible that a significant portion of this is so generated. In the first place, Stewart[19] has pointed out that diagnostic x-rays of the abdomen and pelvis during pregnancy are reported with excessive frequency by mothers of leukemic children. Furthermore, the period of rapid increase in childhood leukemia coincides with the period of marked increase in use of diagnostic x-ray in general and in the use of x-ray pelvimetry in particular.[4] In thinking about this material, it becomes clear that it gives at least an estimate of the maximum incubation period in childhood for the generating event can hardly have taken place before the child was conceived.

This discussion naturally leads to the question as to whether the incubation period for leukemia generated by events other than radiation is likely to be the same as that for the radiation-induced disease. One approach to this problem is simply to say that, having no information to the contrary, we can make this assumption and see if it assists us in future studies. A more constructive approach would be to ask: What is it, in fact, that we are measuring? If one postulates that a specific transformation with survival in one white cell is all that is necessary to initiate the disease, it becomes apparent that we are measuring the period required for one such cell to multiply to the point where symptoms are produced. With this notion, it does not seem reasonable to suppose that the incubation period should be dependent on the nature of the agent producing the initial transformation nor on the dose of that agent. However, Schwartz and Upton[16] have pointed out that in mice the incubation period may be related to the dose of radiation.

Somewhat the same kind of reasoning can be applied to the question about various types of leukemia. It is, of course, possible that certain cell lines might multiply more rapidly than others and it would be extremely desirable to test this hypothesis. At present the available data are not great enough to go beyond saying that no evidence for variation by cell type has been uncovered. In this connection, further study of the situation in early life may reveal complexities not now thoroughly understood. For example, Gilliam and Walter[6] have indicated that the distribution is different for the Negro and have further pointed out that the shape of the age specific curves is changing in ways that are more complicated than would seem to be the case merely on inspection of Fig. 3.

We remain a little uneasy about the cases occurring within a year of the x-ray treatment for spondylitis because 12 months seems such a short period for the time from the first cell to diagnosis, when the period from diagnosis to death averages 4½ months for Court-Brown's experience. Presumably the incubation period should be many times the survival period, for the increase of leukemic cells in the body would naturally be expected to fit a logarithmic growth curve along with other living things.

In any case, it is not inconceivable that special attention to the cases with short incubation periods may prove productive. For example, Reimann and associates[15] have reported that the cases of leukemia diagnosed in the first month of life are predominantly myelocytic rather than lymphocytic as would be expected in the pediatric age group in general. Gunz and co-workers[9] have noted that "similar and distinctive clinical features . . . and hematological findings" are present in cases perhaps up to the age of one year. They raise the question as to whether the etiology in this group may be distinctive as well.

In another approach, Greene[8] has noted a high frequency of separation events in the period immediately preceding the onset of this disease. Since emotional trauma can influence hormonal balance and since hormones may possibly influence the rate of multiplication of leukemic cells, it seems reasonable to ask if emotional trauma may shorten the incubation period of leukemia. If this were found to be the case, it would help to explain Greene's findings without going so far as to suggest that emotional events can generate leukemia. Patient 2 in Graham's[7] material, who was dead of leukemia 8½ months after the first x-ray treatment, is the only one of the 4 cases of short incubation on whom detailed information is available to us. As far as can be determined, this patient did not have any unusually stressful events during the period. Nevertheless, this hypothesis should be examined further. In addition, the possibility that radiation may accelerate the development of a pre-existing leukemia, as suggested by Stewart,[19] should not be entirely overlooked.

It now seems justified to conclude that, from a practical investigative standpoint, it is likely to prove useful to study the period up to 10 years before the onset of clinical cases of leukemia. Those events which occurred unusually frequently in patients as compared with controls should be examined for their specific ability to lead to the type of transformation necessary to generate a malignant disease. For children, the period would seem to be somewhat shorter and there is a suggestion that intrauterine life may be a time of special risk.

These estimates are at best approximate but suggest directions for future research and tend to eliminate the helpless feeling that is apt to confront the investigator of leukemia in his search for cause. Now he need no longer explore the total life experience of his patient nor guess that he need go back only 5 years as was done by Faber.[5]

Beyond the contribution to future research in the field of leukemia, it is felt that a method has been demonstrated which can be applied to other malignant diseases. This method of using x-ray treatment should be applicable to estimating the incubation period for malignant disease of the skin, thyroid, and possibly bone. Perhaps brief exposures to chemicals that are rapidly eliminated from the body would make it possible to estimate incubation periods for some other types of cancer. This is clearly a field which must be more widely explored. The obvious extension of this to include techniques for the continuous exposure case is now being studied.

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SUMMARY

1. The incubation period of radiation-induced leukemia in adults is estimated to be about 5 years with 90 per cent of the cases occurring less than 10 years after exposure.

2. Assuming genesis during gestation, there is a somewhat shorter incubation period for children.

3. If one is willing to assume that the incubation period of leukemia induced by other means is approximately the same, there is now plain indication to search for other causes of leukemia up to 10 years before onset in adults, and during gestation or the first few weeks of postnatal life in the case of children.

4. This approach to the estimation of the incubation period should prove profitable in other malignant diseases.

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Therapeutics

DRUG THERAPY OF THE UNSTABLE BOWEL (Irritable Colon)

A 15-Month Double Blind Clinical Study in 75 Cases of Response to a Prolonged-Acting Belladonna Alkaloid-Phenobarbital Mixture or Placebo

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INTRODUCTION

FUNCTIONAL disease and its somatic manifestations occupy a major part of the efforts of the modern physician. Chronic functional gastrointestinal distress is probably the most prevalent of these disturbances. Improvement in therapy of this condition presents a constant challenge in present-day medicine

Our own experience over a number of years has impressed us with the need for more effective control of these cases. In an initial study we had investigated the clinical effectiveness of an anticholinergic drug (methantheline bromide) in the treatment of the nervous unstable colon.[1] Our conclusions were that this drug was not dramatically effective when compared with a placebo, using the double blind method, and seemed rather to indicate the superiority of a combined belladonna-phenobarbital mixture as an important therapeutic adjunct in management.

PURPOSE AND METHOD

When a prolonged-acting belladonna alkaloid combined with phenobarbital (Belladenal Spacetabs) became available to us, we accordingly set out to evaluate such possible improvement in the therapy of unstable bowel. This was accomplished in a clinical study utilizing the double blind method wherein neither the effective drug nor the placebo was known to patient or physician until the end

This study was supported by Sandoz Pharmaceuticals, Inc., Harry Althouse, Manager, Medical Department, San Francisco, Calif.

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of the study. In addition, we hoped this study would provide us with an answer to the question of the effectiveness of the antispasmodics over any token medication presented to patients in whom the factor of anxiety was uppermost and whose dependency needs were being met by the interest, solicitude, and the authority of the physician.

The patients were those in whom complete histories, physical examinations, gastrointestinal and gall-bladder roentgenologic and laboratory studies either excluded organic disease or indicated that organic disease was inactive at the time. Weekly charts were kept on the progress of the cases. Changes in symptoms were followed and graded. Final judgment was reached on the over-all reaction to the drug in conjunction with a bland diet. The following symptoms were evaluated: generalized abdominal distress, epigastric pain, constipation, diarrhea, heartburn, flatulence (gas), and a general feeling of well-being. Improvement in these 7 categories were graded as to (1) no change, (2) worsening of symptoms, (3) improvement, and in what degree, +1, +2, +3, +4. In addition to the degree of response, the duration of effect was also given due weight in judging the percentage of improvement. Progress charts were utilized with weekly reports ranging from 3 weeks to 3 months. As the study progressed, we gained the impression that the weight of the last item, i.e., the feeling of "gastrointestinal well-being," at times overrode the importance of the other symptoms in the patient's mind in judging the drug's effect. The holistic evaluation thus took precedence over the statistical weight of each complaint. An identically prepared placebo was exhibited in a comparable group of cases drawn from two metropolitan hospital clinics, a group health center, and cases drawn from private practice. Untoward effects of both medications were also noted and tabulated. The Belladenal Spacetabs* were prepared to release active ingredients uniformly over a period of 8 to 10 hours and were administered in the dose of one tablet in the morning and one in the evening. One medication was labeled Belladenal "Y" and the other Belladenal "X." At the termination of the study, the effective Belladenal Spacetab was found to be contained in the "Y" tablet; the "X" tablet was the placebo, containing the innocuous substance.

As the study progressed we gained the clinical impression in a number of cases that Belladenal Spacetab "Y" was the effective medication, and in a small group, when no relief was forthcoming with the placebo "X," we changed the drug to Belladenal Spacetab "Y." Thus one group received both the effective drug and the placebo.

RESULTS

The total number of patients studied by both observers was 75 cases. The effective drug was used alone in 43 cases; the placebo was used alone in 20 cases. In 12 patients successive trials were carried out employing the placebo and effective drug.

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*Belladenal Spacetabs (Sandoz) composition: total levorotatory alkaloids of belladonna as malates (Bellafoline), 0.25 mg.; phenobarbital, 50 mg. Bellafoline comprises the total levorotatory alkaloids of belladonna, principally l-hyoscyamine, the form which is claimed to be the pharmacologically active one.

No attempt was made to alternate cases on the drugs by either observer. The greater number of trials with the active drug (Y) may be partially explained by the fact that since it became evident in the early weeks of administration that the "X" drug was ineffective in a number of cases, we were prompted to substitute the apparently effective drug. This factor influencing the clinical evaluation of drug in the double blind method has recently been commented upon by Modell and Houde.[10]

An attempt was made at quantitation of the effect of the two medications on the specific symptoms chosen for evaluation of improvement during the period of observation. Tables I, II, and III present data on the number of cases presenting each symptom and the relative degree of improvement in each with both drugs when given in separate patients and Table IV presents data on the 12 cases in which both drugs were administered in alternate periods.

It is of interest that the mean percentage of patients improved in all categories in both groups of cases receiving the effective drug was 75.6 per cent as against 29.8 per cent for the placebo. When the patients were evaluated from the "holistic" point of view of a clinical judgment of the total response of the patient as based on the critical appraisal of each observer with reference to a general feeling of well-being and improvement, 69 per cent were judged improved

TABLE I. DEGREE OF RESPONSE OF SPECIFIC SYMPTOMS TO EFFECTIVE DRUG (43 PATIENTS)

	DEGREE OF IMPROVEMENT						TOTAL PERCENTAGE WITH IMPROVEMENT
	+4	+3	+2	+1	0	WORSE	
Generalized abdominal distress	27.2%	24.1%	34.5%	10.3%	14%		86
(29 patients)	(5)	(7)	(10)	(3)	(4)		
Epigastric pain	15%	30%	30%	20%	5%		95
(20 patients)	(3)	(6)	(6)	(4)	(1)		
Constipation	9.5%	9.5%	28.5%	4.7%	47.6%		53.2
(21 patients)	(2)	(2)	(6)	(1)	(10)		
Diarrhea	50%	33.3%	16.6%				100
(6 patients)	(3)	(2)	(1)				
Heartburn	21.4%	21.4%	21.4%		35.7%		64.3
(13 patients)	(3)	(3)	(3)		(4)		
Flatulence	12.9%	19.3%	45.1%	12.9%	12.9%		87.1
(31 patients)	(4)	(6)	(13)	(4)	(4)		
General well-being	15.3%	19.2%	42.2%	15.3%	7.3%		92.7
(26 patients)	(4)	(5)	(11)	(4)	(2)		

TABLE II. DEGREE OF RESPONSE OF SPECIFIC SYMPTOMS TO PLACEBO (20 PATIENTS)

	DEGREE OF IMPROVEMENT						TOTAL PERCENTAGE WITH IMPROVEMENT
	+4	+3	+2	+1	0	WORSE	
Generalized abdominal distress		15.7%	15.7%	5.2%	63.1%		46.9
(19 patients)		(3)	(3)	(1)	(12)		
Epigastric pain		7.14%	21.4%		71.43%		28.57
(14 patients)		(1)	(3)		(10)		
Constipation		14.28%	28.56%		57.16%		42.84
(7 patients)		(1)	(2)		(4)		
Diarrhea		33.33%			66.66%		33.31
(6 patients)		(2)			(4)		
Heartburn		14.3%	14.3%		71.43%		28.57
(9 patients)		(1)	(1)		(7)		
Flatulence		14.3%	21.43%	7.15%	57.4%		42.6
(14 patients)		(2)	(3)	(1)	(8)		
General feeling of well-being			15.4%	15.4%	69.2%		30.8
(13 patients)			(2)	(2)	(9)		

TABLE III. COMPARISON OF PERCENTAGE OF CASES WITH IMPROVEMENT

	Y CASES (EFFECTIVE DRUG)		X CASES (PLACEBO)	
	43 PATIENTS	12 PATIENTS	20 PATIENTS	12 PATIENTS
	SINGLE COURSE	DOUBLE COURSE	SINGLE COURSE	DOUBLE COURSE
Generalized abdominal distress	86.0	55.5	46.9	0.0
Epigastric pain	95.0	55.0	28.5	11.1
Constipation	53.2	22.0	42.8	0.0
Diarrhea	100.0	33.0	33.3	0.0
Heartburn	64.3	50.0	28.57	50.0
Flatulence	87.1	72.0	42.6	50.0
General feeling of well-being	92.7	55.5	30.0	11.1
Percentage of improvement	82.3	49.0	36.0	17.4
Over-all effectiveness	Effective Drug 75.6		Placebo 29.8	

TABLE IV. EFFECT ON SYMPTOMS IN 12 PATIENTS GIVEN ALTERNATE COURSES OF PLACEBO AND EFFECTIVE DRUG

	PLACEBO							EFFECTIVE DRUG						
	DEGREE OF IMPROVEMENT						TOTAL PERCENTAGE WITH IMPROVEMENT	DEGREE OF IMPROVEMENT						TOTAL PERCENTAGE WITH IMPROVEMENT
	+4	+3	+2	+1	0	WORSE		+4	+3	+2	+1	0	WORSE	
Generalized abdominal distress					100%		0.0		22.2%	33.3%		44.4%		55.5
(9 patients)					(9)				(2)	(3)		(4)		
Epigastric distress				11.1%	88%		11.1	11.1%	22.2%	11.1%	11.1%	44.4%		55.5
(9 patients)				(1)	(8)			(1)	(2)	(1)	(1)	(4)		
Constipation					100%		0.0	11.1%			11.1%	88.8%		22.2
(10 patients)					(10)			(1)			(1)	(8)		
Diarrhea					100%		0.0				33.3%	66.6%		33.0
(4 patients)					(4)						(1)	(2)		
Heartburn			50%		50%		50.0		25%	25%		50%		50.0
(6 patients)			(3)		(3)				(1)	(1)		(2)		
Flatulence			33.3%	16.6%	50%		50.0	9.1%	27.2%	9.1%	27.2%	27.2%		72.0
(12 patients)			(4)	(2)	(6)			(1)	(3)	(1)	(3)	(3)		
General feeling of well-being				11.1%	88.8%		11.1	11.1%	22.2%	22.2%		44.4%		55.5
(9 patients)				(1)	(8)			(1)	(2)	(2)		(4)		

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with the effective drug and 24 per cent with the placebo. These evaluations were arrived at following a study of the factors in the narrative case history compiled in each case during the period of study.

The symptom of chronic constipation was an outstanding and difficult problem in many instances. This symptom failed to be affected or improved by Belladenal Spacetabs in 7 of 9 cases in which this was a prominent complaint. Two cases reported a considerable response in this regard together with the other symptoms. It was therefore found necessary to supplement the therapeutic regimen with bulk producers and mild laxatives.

The incidence of side effects was studied by both observers. Xerostomia was observed in 7 of the cases treated with the effective drug (11 per cent) and in 4 of the cases with the placebo (12 per cent). Mydriasis was encountered in 2 cases in the effective drug series and in 2 cases where the placebo was employed. An occasional side effect in both series was an aggravation of an existing symptom of heartburn. Other side effects were negligible.

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It was of some interest that, in the cases benefited by the placebo, the response was observed to occur rather quickly and with immediate effect. The recrudescence of symptoms in this group occurred in an equally rapid manner. In one case in which the placebo and the effective drug were exhibited in succession, the patient's evaluation was that the former was "good," but that, when the effective drug was given in successive weeks, this was "even better." A strong psychosomatic overlay with severe generalized anxiety was considered to be present in 11 cases. It was noteworthy that of this group, 9 (81.8 per cent) failed to respond to the effective drug. When the anxiety component was severe, we found that the additional use of centrally effective medications (mood-ameliorating drugs and tranquilizers) was required.

An attempt was made to determine the effectiveness of other similar pharmacologic medications for purposes of comparison. In 10 patients to whom the effective drug was administered, comparable antispasmodics and sedative combinations had been given in the past for the same symptoms. It was admittedly difficult to apply strict criteria for evaluation, but benefit was reported in varying degree from these other preparations in 7 cases, while in 2 no improvement was noted. In one patient, diarrhea was present in association with the upper bowel symptoms and was simultaneously benefited. One practical advantage of the Spacetabs over the other preparations may derive from its prolonged acting effect, requiring only 2 tablets daily, 12 hours apart.

Indicative of the diversity of associated gastrointestinal conditions present in our cases of unstable colon were histories of chronic peptic ulcer, severe hypertrophic gastritis, diverticulosis, paraesophageal hiatal hernia, and intercurrent attacks of gastrointestinal hemorrhage from duodenal ulcer.

CASE REPORTS

The following 7 cases were chosen from the series for individual consideration since they serve to illustrate specific situations encountered in the course of the use of the medication.

The first case is an example of a functional gastrointestinal tract disturbance with predominant involvement of the large bowel and is typical, both in clinical pattern and in response to treatment, of those favorably affected.

CASE 1.—L. H., a white woman, aged 25 years, complained of dull "aching" over the entire abdomen, with cramplike distress in both lower quadrants, for several years. The pains were intermittent and at times occurred during the night. These were occasionally associated with mild diarrhea. At other times the bowel state was either normal or mildly costive. Occasional attacks of excessive abdominal gas had occurred of late. Complete gastrointestinal x-ray and laboratory studies were negative, as were repeated stool examinations. Proctoscopic examination revealed no mucosal changes. A bland diet prescribed previously had been conscientiously followed, but without benefit. No situational psychosomatic factors seemed operative. On the Belladenal placebo (X) regime she noticed no benefit and demurred when Belladenal Spacetabs (Y) were recommended. She finally consented and was surprised to find a satisfactory remission of the abdominal distress, distention, and borborygmus; the mild constipation persisted at times but was finally relieved to a great degree by dietary adjustment. Following this, the patient added that mild dietary indiscretions no longer seemed to be upsetting.

Case 2 is an example of inprovement of a functional disturbance of the alimentary tract with symptoms limited to the upper gastrointestinal tract.

CASE 2.—R. M., a 42-year-old woman, had been treated for a duodenal ulcer in 1952 and 1953 with characteristic remission of symptoms. Six months after a hysterectomy in 1956 she began to suffer from a persistent burning in the epigastrium, often occurring at night, and relieved by sitting up, by milk, or by a "tranquilizing" drug. Recent gastrointestinal roentgenograms were negative for duodenal ulcer and for hiatal hernia. For 2 weeks before admission the pain was more intense and was present "almost constantly." There was no constipation, flatulence, distention, or borborygmus. She listed as previous attempts at therapy the following: bland diet, frequent feedings, occasional Donnatal administration, various antacids, and psychotherapy. No situational factors appeared to be playing a role. Physical examination was noncontributory. A mild secondary anemia was the only positive laboratory finding. After discontinuing all previous medications, she was advised to remain on a bland diet, with Belladenal Spacetabs (Y) every 12 hours. Gradual improvement ensued, until 2 months later the pain had almost entirely disappeared and the patient was experimenting with a more liberal diet.

Cases 3 and 4 represent examples of an effective blockade of the anticholinergic drug effectiveness by a strong psychosomatic overlay.

CASE 3.—L. W., a 38-year-old white woman, complained of persistent severe left lower quadrant pain, abdominal distention, and chronic constipation with occasional episodes of mild diarrhea. The stools during the constipative phase were ribbony or pellet-like. In addition she described a feeling of air hunger, weakness, vertigo, various paresthesias, a sensation of excessive fluid in the scalp, and other bizarre manifestations indicative of a somatic neurosis. Despite anorexia and nausea her weight remained strikingly static. Physical examination and gastrointestinal x-ray studies were essentially negative. On a bland diet with Belladenal Spacetabs (Y) twice daily she failed to obtain any relief; however, on a placebo there was partial improvement for several weeks in most of her symptoms.

CASE 4.—R. R., a 48-year-old white woman, was admitted to the Cedars of Lebanon Gastrointestinal Clinic with symptoms of alternating constipation and diarrhea, diffuse abdominal cramping, frequent emesis, marked air hunger, frequent attacks of weakness, and occasional syncope. She had been examined by many of the clinic staff members during the past 5 years and had had repeated gastrointestinal x-ray, laboratory studies, and sigmoidoscopies, with no evidence of organic disease. She was placed on a Belladenal-bland dietary regime, with the understanding that although it might not help many of her unrelated symptoms it might be of value for those complaints related to her irritable gastrointestinal tract. However, there was no response whatever to either Belladenal or its placebo counterpart.

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Case 5 is a striking instance of the powerful effect of a placebo (X) in a patient with a pronounced "mucous colitis."

CASE 5.—P. B., a 67-year-old white woman, who was first seen Aug. 15, 1956, with a history of the passage of voluminous amounts of mucus for 2½ years, chronic constipation, and obvious free-floating anxiety. Of interest is the fact that in 1927 her husband, who had been a prominent physician, divorced her suddenly and married his secretary. She had never become reconciled to this loss of status, and her gastrointestinal symptoms dated from this period onward. Previous treatments had included, among others, tincture of belladonna and phenobarbital, bile salts, milk of magnesia, sodium phosphate, and repeated enemata every other day. The latter were resorted to even when traveling. In August, 1954, long "white cords" appeared in the stool, along with the chronic constipation, and this mucus, which she reported appearing in "gobs and gobs," continued during 1955 and 1956. In this period she appeared well preserved, preoccupied with her symptoms, rather depressed, and without any significant weight loss. From July 11, 1956, she was given a combination of extract of belladonna and phenobarbital. On Aug. 15, 1956, when her condition remained unchanged, Belladenal placebo (X) was administered. She returned 2 weeks later very concerned over the cessation of the "mucus" wondering where it was going since it had disappeared, even though she was still constipated. During September she was still constipated, but the mucus did not reappear until later in the month and in much less amount. She continued with the use of the placebo until January, 1957, with no trace of the mucus. The residual constipation later proved amenable to bulk producing agents.

Cases 6 and 7 are examples of the relief of a predominant extracolonic symptom (heartburn) in functional disturbances of the alimentary tract.

CASE 6.—M. F., aged 55 years, complained of persistent heartburn, epigastric burning 2 to 3 hours after meals, left lower quadrant cramping, and epigastric night pain relieved by food and alkali. The bowel state was normal. Roentgenograms and laboratory studies of the upper and lower gastrointestinal tract were negative for organic pathologic change. Although a frequent-feeding, antacid regime gave considerable relief, the heartburn persisted. Following the administration of the effective Belladenal Spacetab (Y) every 12 hours, the heartburn gradually subsided.

CASE 7.—J. T., aged 60 years, was admitted to the Outpatient Clinic because of persistent severe heartburn which often awakened him between 4 and 6 A.M. for several months. No other symptoms except a mild constipation were present. Roentgen studies of the gastrointestinal tract revealed no evidence of ulcer, but a small hiatal hernia and a midesophageal diverticulum were demonstrated. A frequent-feeding regime with 45 degree back rest elevation at night, and the exhibition of amphoteric substances had no effect on his distress. However, 3 weeks after starting the regime with the effective Spacetab his heartburn had entirely subsided. The constipation remained unimproved.

DISCUSSION

Any seasoned clinical investigator who sets out to evaluate the effectiveness of a single drug in a functional disturbance, such as "indigestion," is aware that his study may be fraught with pitfalls. While he is honestly attempting to exercise sound and objective judgment during the progress of the study, diverse factors, of varying intensities, and beyond his ability to control, are at play.

The physician's influence unquestionably depends in part on his personality, and should be recognized as a potent influence. This has been well put by Hardin, Levy, and Seager[2] in a study similar to ours in which they state that the Bellafoline derivatives are valuable as adjuncts in relief of symptoms, "but as yet fail to be the panaceas first acclaimed. Nor can they even replace the physician's warmth of understanding and interest in all the problems of his

patients." A discussion of the usefulness of any drug employed in this area should thus be viewed in the light of the considerations discussed.

The nonpharmacologic variables which include the effect of the doctor-patient relationship and the impact of psychologic changes in the patient have been recently emphasized by Shapiro and Teng[3] in a drug assay study in the hypertensive patient.

The terms "irritable colon" and "unstable colon" are commonly accepted designations for functional colon disturbance. However, it must be remembered that in patients in whom an imbalance of the autonomic nervous system exists, the colonic aspects may not be readily recognizable or may be negligible. Motor disturbances elsewhere are often more intense and may be variously described as "pylorospasm," "irritable pylorus or duodenum," increased gastric tonus, and hyper- or hypomotility. Purely motor derangements of the small bowel play a factor in many cases. Kalser, Zion, and Bockus[4] state that the concept of the spastic colon should be broadened to include that of a generalized neuromuscular irritability of the entire alimentary tract. There is need therefore for a more informed clinical classification and subgrouping which would provide dividends in terms of more effective therapy. As this study progressed it became clear that this medication served as a therapeutic tool in delineating two such subgroupings, that of an "upper bowel functional syndrome" and a "lower bowel functional syndrome." The former constellation of symptoms which responded rather well to the drug under study consisted of one or more of the following: flatulence, heartburn, epigastric distress, "gas," gaseous distention, frequent eructations, aerophagy, food intolerance, fullness, and peristaltic unrest. The major symptoms characterizing the "lower bowel syndrome" were: chronic constipation of long-standing, pain and tenderness in both lower quadrants, and a dependency on laxatives of different kinds, each of which in time failed to overcome the recalcitrant character of the constipation. In an occasional case this symptom of constipation appeared to respond to the Belladenal Spacetabs alone. However, in most, adjunctive treatment, bulk-producing agents, or laxatives, were required.

The effect of cholinergic-blocking agents on gastric and colonic motility and colonic spasm have been investigated by many workers in both the experimental and clinical fields. In an experimental comparison of the effect on the human small intestine of Bellafoline, atropine, scopolamine, and papaverine, Kramer and Ingelfinger[5] found that Bellafoline occupied first place in terms of decrease in tone, diminution of peristalsis, and duration of effect. The reduction of the cramplike distress of the irritable colon following the administration of atropine or its derivatives in suitable dosage has long been known.

Of interest, however, is the effect of these drugs on patients presenting other predominant symptoms less well defined physiologically, but of more immediate moment from the patient's point of view, i.e., abdominal distention, borborygmus, and heartburn, particularly the latter. It is fairly obvious from recent studies that the relief which follows antacids in heartburn is not due to neutralization of acid. Chester Jones[6] has been able to reproduce heartburn in 50 per cent of cases by balloon distention of the lower esophagus and a neuromuscular dis-

turbance of the area appears the most likely etiologic mechanism. Likewise borborygmus when not associated with obstructive symptoms is probably the result of disturbed intestinal motility. We were impressed again in this study with the observation that, in those cases in which a prominent psychosomatic overlay existed, the anticholinergic effect appeared on clinical grounds to be effectively negated. This pattern of response appeared to be consistent in 9 of our cases. This may represent a clinical demonstration of Almy's[7] experiments with the blocking of anticholinergics by emotionally charged interviews and by insulin administration. We[1] have observed that the anticholinergic agent may be relatively more effective in those patients in whom the aggressive component was the least predominant element of the anxiety state. Werner and his coworkers[8] point out that the effectiveness of atropine, prostigmine, and Pitressin is modified by induced emotional stress and that the emotional state of the patient at the time the drug is administered determines to some extent the effectiveness of the oral therapy. Atropine has been shown to have little effect on the musculotropic spasm and is at ordinary dosage unable to block the effects of acetylcholine on the autonomic ganglia.

In their discussions of the colon under stress, Grace, Wolf, and Wolff[9] observed that overwhelming life situations provocative of abject fear and dejection were associated generally with hypofunction of most of the large bowel with relative lack of contractile activity, while those provocative of conflict with manifestations of anger, resentment, hostility, and anxiety were associated with hyperfunction, increased peristalsis, and sustained contractions of longitudinal muscles of the colon with shortening and narrowing of the lumen and intense and frequent waves in cecum and ascending colon. Almy[7] feels that the causes for the unstable bowel can be classed under four headings: (1) life stress and emotional conflicts, seen in 60 per cent of cases and indicated experimentally by gastrointestinal motility kymograph studies during interviews on "emotionally charged" subjects, (2) misuse of laxatives and cold fluids, (3) allergy, and (4) previous organic disease (residual organic or psychiatric disease).

The effectiveness of placebos in functional gastrointestinal distress as well as in peptic ulcer treatment has been reported as between 30 and 40 per cent. Our figures of 75 per cent usefulness of the Belladenal preparation as against a 29 per cent response to the placebo would suggest that, while the ultimate in effectiveness is a goal yet to be attained, this preparation can be looked upon as a useful adjunct implementing the over-all therapeutic regimen in this area of functional disease.

SUMMARY AND CONCLUSIONS

1. Seventy-five cases with active symptoms of the unstable bowel were treated by two clinicians over a 15-month period with a prolonged-acting levorotatory belladonna alkaloid and phenobarbital combination (Belladenal Spacetabs) or placebos, employing the double blind method with a bland diet.

2. Of the cases treated with the effective drug, 75.6 per cent were benefited by the medication based on an evaluation of the degree of response of a typical

constellation of symptoms. Of the cases treated with a placebo, 29.8 per cent were beneficially influenced.

3. Where extreme anxiety and agitation were superimposed on the gastrointestinal symptoms, effective blockade of drug effect was encountered.

4. This drug study served clearly to delineate symptoms referable to the unstable digestive tract into an "upper bowel syndrome" and a "lower bowel syndrome"; the most prominent symptom of the latter, chronic constipation, failed to respond to the medication.

5. The power of the placebo in isolated but dramatic instances in influencing deep-seated symptoms of long-standing such as "the mucous colon" was documented in this study.

6. Antispasmodic-sedative medication has a rightful adjunctive position in therapy. Prolonged-acting preparations recommend themselves from the practical standpoint.

7. The therapy of the unstable bowel is a multifaceted one in which the interplay of psychic factors operative within the framework of the patient-environment-physician relationship, the allaying of the anxiety and tension state, and diet all play a part.

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HOSPITAL-BASED PREHOSPITALIZATION HOME CARE

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THE concept of home care has gained, in recent years, considerable eminence as an extension of hospital services.[1-9] Hospital-based home care has demonstrated itself as an effective means of providing necessary medical as well as allied medical services without incurring either the physical separation from home and loved ones or the severe economic strains of hospital care. It is a supplement to hospital care that is now widely accepted as a medical care innovation of great flexibility. Home care places an instrument into the hands of hospital administrators and clinical physicians which has produced profound effects upon the outcome of treatment, the availability, the utilization, and turnover of hospital beds and upon the basic relationships of hospitals to their patients. By choosing to transfer a patient from hospital to home care, the physician is able to make a decision, the net effect of which is to provide a more appropriate, efficient, and humane medical care regime for those patients no longer deemed to require the type of concentrated medical services available only in a modern hospital. It seems apparent that hospital-based home care will continue to expand its influence in the field of posthospitalization medical facilities.

The entrance of home care upon the scene of American medicine has come at a propitious time. Even had the major problems confronting medicine today continued to be those of acute illnesses, home care should have been welcomed as an adjunct service for the recuperative and convalescent phases of care required. But in this day, with the prevalence of chronically ill persons increasing rapidly,[10] the concept of home care offers potentialities of medical care of unprecedented magnitude. One such potentiality is an adaptation which is the subject of this paper: prehospitalization preventive maintenance and rehabilitation.

The monumental task of caring for patients with long-term illness has been widely discussed.[10] It has fallen to the nation's 9,000 hospitals with their 1.7 million beds to provide a substantial portion of care for these patients. Despite the rapidly increasing number of chronically ill (estimated at 5.3 million persons[11]),

accretion of hospital beds explicitly for their care has not kept pace.* Consequently, it is the general hospital which has become, by default, the basic medical facility for the care of large numbers of chronically ill persons. Most commonly the inpatient medical services of general hospitals will accept a patient for service only if his condition is sufficiently serious to warrant hospitalization for diagnosis and/or treatment during an acute or moderately advanced stage of his ailment. Hospital care of the chronically ill frequently requires prolonged treatment, the cost of which can be fully borne by relatively few people. There would be little problem were all chronically ill persons not requiring the intensive type of care given in hospitals, able to receive such attention as is needed in outpatient clinics. A major problem arises, however, because of the fact that a substantial number of patients neither require hospitalization, nor are they at the same time capable of the minimal ambulation necessary for continuing care as outpatients. It is a well-known fact that the inadequacy of transportation services to and from hospital clinics prevents a good many patients from benefiting from this type of care even if wheelchairs or other forms of ambulation aids are available. It is for such patients especially that prehospitalization home care would be most beneficial.

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What then is prehospitalization home care? Simply stated, it is the provision of home care, hospital-based, medical and allied medical services to patients requiring these services but not necessarily within the physical limits of the hospital. It is a method of providing the advantages of hospital care without its disadvantages, namely, the isolation and separation of the individual from his natural surroundings and the exceptionally high economic burdens imposed by the high cost of medical care. An ideal prehospitalization home care program would include, in addition to medical and nursing services, as required by the particular case, physical and occupational therapy, social case work, clinical psychology, laboratory facilities, and homemaker services. These latter might include a meals-on-wheels service as well as a shopping service for families unable to leave the household. Medical specialists would be provided as necessary and, should the patient's condition warrant it, inpatient hospital care would be provided.

The value of prehospitalization home care would seem to include the following points: (1) It would provide for necessary long-term treatment of patients with chronic illnesses not requiring hospitalization but continuous medical and allied medical services. As the Commission on Chronic Illness has indicated, adding hospital beds is not the most desirable method of dealing with the problems of an increasing chronically ill population. Thus, "overemphasis has long been given to institutional care of long-term patients as the solution of their problems. Even though less than one-fourth of the patients are in hospitals and other medical institutions, many of the ones who are in such places could—under suitable conditions—be cared for as well or better, and more economically, at home.

*According to figures released by the Department of Health, Education and Welfare, at present there are 44,137 beds for chronic illness (nonmental disease) in the United States of which 6,648 are nonacceptable (beds in a building deemed unsuitable for use or a public hazard). Estimated need for new beds in this category is more than 308,000.

It is true that construction of additional facilities is needed, particularly for patients needing rehabilitative services and those whose need is primarily for skilled nursing care. More and more beds for long-term care, however, will not solve our basic problem."[10] (2) It would tend to off-set the deterioration and crippling which frequently accompany prolonged illness which is not kept under direct medical surveillance. (3) Related to this factor is the practicability of preventing the deterioration of psychologic status and morale by active treatment in conducive surroundings. (4) The potentialities of rehabilitation of such persons may be significantly increased by instituting a program of rehabilitative home care *before* the long-term effects of the illness make the process irreversible. (5) For those patients who, because of their condition, must await hospitalization in a chronic illness institution, prehospitalization home care would serve to provide the necessary medical and allied facilities at a comparatively early stage of the person's illness. Thus, this program would tend to decrease the potential time necessary for hospital care, making for a greater turnover of hospital beds. (6) The program would allow greater flexibility in making medical decisions regarding the need for outpatient care, institutional care, or home care, permitting the more appropriate utilization of hospital bed services. (7) The program would permit individuals who normally would have to be transferred to hospitals to remain at home among their own family and loved ones receiving continuous medical care and in the type of environment which should prove psychologically appropriate to recuperation and rehabilitation. Patients so maintained at home, through vocational counseling and prevocational preparation in occupational therapy, may become semi-independent. This may be accomplished by an appropriate program of homework, thus contributing to self and family support. (8) The prehospitalization home care program essentially is an attempt at preventive maintenance and preventive rehabilitation, services which should prove far less costly than hospitalization. (9) In this connection such a program should prove beneficial to the management of indigent patients requiring long-term care (patients who tend to feel rejected and abandoned), whether or not such patients are under the supervision of a governmental or voluntary hospital. (10) Prescriptions for necessary drugs could be filled by the hospital pharmacy. Even a dental care program could be introduced as part of the total care given.

It might be argued that a prehospitalization home care program might tend to encroach upon the private practice of medicine. It should be clear from the description given above that the average private practitioner normally could not be expected, nor is he able, to provide the special kinds of rehabilitation services necessary for the home management of patients with long-term illness. Nevertheless, the patient's own physician may continue to care for him both for services normally necessary to the patient at home as well as to provide continuity of care. The program would be activated at the request of the individual physician for those patients deemed to have been given the maximum private medical care or for whom private medical care is not possible. In this connection it may be pointed out that the majority of chronically ill and disabled patients are medically, if not financially, indigent. Patients with multiple sclerosis, muscular dystrophy, cancer,[12] advanced diabetes, rheumatic

and other forms of heart disease,[13] cerebral palsy, arthritis and rheumatism, and other types of neurologic, muscular, and metabolic disorders could be managed under a program of prehospitalization home care. Such a program would increase the medical powers of a chronic illness institution and would greatly enhance the medical care programs of general hospitals.

Prehospitalization home care including preventive maintenance and rehabilitation combines the interests of preventive medicine, clinical medicine, and rehabilitation medicine. It offers itself as a mechanism increasing the flexibility of medical care programs providing more appropriate medical facilities for those patients requiring such care, eliminating the problem of transportation to and from outpatient clinics while maintaining optimal medical management of each case, and for reducing hospital costs.

A program of prehospitalization home care necessarily would require the coordination of medical and nursing as well as welfare facilities in the community in which it is established. Although the base of the operation would be in the hospital, preferably a chronic illness hospital, community nursing and social welfare services should be made available to such patients on the same basis as is currently true for those receiving posthospitalization home care.

The program described should also prove useful in the education of undergraduate medical and graduate medical students. Here the student and young physician would come into contact with patients who largely will not have had inpatient hospital care. Management of the case would be conducted in the individual's home and such experience should prove salutary in the preparation of the physician for private practice, a goal of the "comprehensive medicine" movement. Being able to perceive the relationship of the individual to his natural surroundings, the physician should be in a better position to provide medical guidance in line with the practical considerations of everyday living. In addition, since the care of the chronically ill patient requires the most intimate relationships between the physician and other members of the medical team, training in such interdependent work should also prove valuable.

The concept of home care as currently functioning has proved an invaluable adjunct to existing medical services. A further variation of this concept, namely, that of prehospitalization home care suggests itself as a measure designed to increase the strength of the hospital by offering home services of a preventive and rehabilitative nature for those patients not requiring long-term hospitalization, but either continuous or intermittent medical care. Such a program should prove useful in the management of patients who are not ambulatory and who, therefore, are unable to reach outpatient clinics. It may also be used to deal with patients having advanced diseases who likewise cannot be moved but for whom hospital care is largely unnecessary. Since prehospital home care offers the possibility of home training and home work, the program would be beneficial in keeping the patient meaningfully occupied with a sense of semi-independence while helping toward paying part of the costs of the program. The savings to the individual in terms of his ability to remain undisturbed in his own household and to the community in terms of its ability to offer ample medical services at

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a considerably reduced cost merits the careful attention of all those interested in the adaptation and expansion of medical services in a population whose major medical characteristics demonstrate an increasing concentration of chronically ill patients throughout the population.

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Book Reviews

CREATIVE USE OF SHELTERED WORKSHOPS IN REHABILITATION. Report of an Institute Held for Regions I and II, Federal Office of Vocational Rehabilitation. Under the Auspices of Altro Health and Rehabilitation Services, Inc. New York, Sept. 9 to 13, 1957. Price 50 cents. Pp. 47.

As the subtitle indicates, this is a brief report of the highlights of an institute held to orient and instruct state agency staffs and consultants in the philosophy and use of sheltered workshops in rehabilitation.

It is not possible to convey in such a report what the participants and trainees no doubt gained from the institute, particularly since part of the experience was a visit to 8 selected sheltered workshops representative of skilled leadership in the use of such a setting in the varied aspects of the rehabilitation process.

The report should be useful to those working in the various phases of rehabilitation to stimulate thinking and planning for such programs in their communities.

Florence Mahoney

WATER AND ELECTROLYTE METABOLISM IN RELATION TO AGE AND SEX. Ciba Foundation Colloquia on Ageing, Vol. 4. Edited by G. E. W. Wolstenholme and Cecilia M. O'Connor. Boston, 1958, Little, Brown & Company. Pp. 327, indexed. Price $8.50.

The attitude of the medical scientist is conditioned by the times, and this is the age of the organization man. So we have congresses, colloquia, and interdisciplinary festivals. Not all of these, of course, are evil in themselves. No one can deny the value of exchange of ideas and it is possible to believe that the participants had fun. But one wonders from time to time what impulse compels publication of the deliberations, formal and informal. The formal papers frequently refer to unpublished experiments and these so scantily that, since the manuscripts have not passed through the rigorous refereeing process imposed by every competent journal, the reader cannot wean data from desire.

Having relieved myself of generalities I admit that there are distinguished exceptions and this, perhaps, is one. The title is misleading. There are a number of papers, having nothing in particular to do with age or sex, which are lucid, pithy reviews of the current state of knowledge or opinion in various branches of the study of salt and water metabolism. These include: Davson's "Cellular Aspects of the Electrolytes and Water in Body Fluids," which begins with a simple treatment of the Gibbs-Donnan equilibrium system and discusses body electrolyte anatomy and some mechanisms for producing gradients in ion concentration between cells and interstitial fluid; Fourman's and Leeson's critical review of causes and manifestations of hyper- and hyponatremia; Black's "Renal Function in Respiratory Failure," somehow accomplished in only four pages and not as informative as this knowledgeable man can be; and Fejfar's "Water and Electrolyte Metabolism in Congestive Failure," which, besides being a straightforward review of fairly well-known observations, happily includes much of his own work not otherwise easily available to American readers.

In a second category may be placed those reviews of the development of certain regulatory functions. Adolph's "The Development of Physiological Regulation of Water Content" summarizes a stimulating series of inquiries. Widdowson and McCance review the development of

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acid-base control. Kerpel-Fronius, the father of interest in electrolyte problems in pediatrics, reviews the reasons for and consequences of the infant's peculiar susceptibility to these disorders.

In a third group are 10 papers bearing on the relation of water and electrolyte metabolism to hormones, including those of sex, and to aging, as opposed to development. In the main, these latter have to do with descriptions of the limited ability of aged organs to continue the nice regulation of water and electrolyte metabolism. Finally, in the miscellaneous category, there is a report of a case of magnesium deficiency in a very sick patient whose symptoms are difficult to disentangle.

All in all, there are 23 chapters in 317 pages. For toilers in the vineyard the reviews add little that is new. For the generally interested the reviews are convenient, concise summaries by a first-rate group of investigators.

Kenneth L. Zierler

MYASTHENIA GRAVIS. By Kermit E. Osserman, M.D., F.A.C.P. New York and London, 1958, Grune & Stratton, Inc. Pp. 286, indexed. Price $10.00.

This book fills the need for a summary of present knowledge of the pathologic anatomy and physiology as well as the clinical management of myasthenia gravis. The author presents both sides of controversial points. Extensive references are cited and the index is well organized. This text should prove helpful to the physician confronted with the problems associated with the care of the myasthenic patient.

Richard J. Johns

READINGS IN MEDICAL CARE. Edited by the Committee on Medical Care Teaching of the Association of Teachers of Preventive Medicine. Chapel Hill, 1958, University of North Carolina Press. Pp. 708, indexed. Price $6.50.

This is an anthology prepared by an ad hoc committee (the names of its members are not given) of the Association of Teachers of Preventive Medicine. It is undoubtedly true that, as the preface states, a significant need will be filled by the book. The teaching of preventive medicine to medical students can probably be said to be the most difficult demand placed on a medical faculty. Not only are the content and approach different from what all the student's other work prepares him for but rather few faculty members are of the turn of mind optimal for such teaching. Sound textbooks and source books can be of great assistance. The lack of such in the past has been one of the reasons for the pedagogic difficulties.

Some of the topics covered are industrial health programs (such as that of the United Mine Workers), home care programs, group practice, what the general practitioner does in rural and in urban areas, nursing homes, workmen's compensation, multiphasic screening, voluntary and government subsidized health insurance, and rehabilitation.

Much of the material would probably, in this country at least, not have been construed as preventive medicine 20 years ago or even more recently. The predominant and quite proper concern with the socioeconomic aspects of medicine is the basis for the designation Department of Social Medicine, or Department of Social and Preventive Medicine, as used in many universities in the United Kingdom. Alas, in the United States the fearsome vision of socialism conjured up by this title does not permit such honesty.

Victor A. McKusick

APHRODISIACS: FROM LEGEND TO PRESCRIPTION. By Alan Hull Walton. Westport, Conn., 1958, Associated Booksellers. Pp. 267, indexed. Price $7.95.

There ought to be a law against books with titles that titillate but prose that petrifies. This nonerotic opus is so bad that its essential flavor cannot be captured in words allowed in a journal that caters to the family trade. Here are some choice passages, however:

"The impotence of over-driven brain-workers, mathematicians, and so on, has become almost proverbial."

"Mild flagellation is, to say the least, undesirable, for it may easily lead to a vicious and compulsive form. . . ."

". . . in coition Hindus will drink sherbet, chew betel-nut, and even smoke."

"Modern pharmaceutical genital tonics and stimulants find a ready sale in India, and the quacks, with their infinitely less reliable nostrums, make easy fortunes."

"The aphrodisiac effect of bird nest soup cannot be denied."

"Some of the most satisfying lovers have possessed organs even slightly below average."

There are also some 20-odd pages containing recipes for onion soup, banana beefsteak, fried cuttle fish, egg flip, Madeira trifle, Spanish caper sauce, and other genital battery-chargers.

Louis Lasagna

A HISTORY OF NUTRITION. By Elmer Verner McCollum. Boston, 1957, Houghton Mifflin Co. Pp. 451, indexed. Price $6.00.

In 1745 Beccari concluded that man (except for the spiritual portion of his being) was composed of wheat gluten. Nutrition has traveled an enormous distance in the last two centuries, and there are few workers in this field whose contributions equal those of Dr. McCollum. His wisdom and experience, conjoined with a delightful literary style, make this book a pleasure to read. Of particular interest to me were the sections on food fads through the centuries. The list of "thorough mastication" advocates, for example, included Count Rumford, Brillat-Savarin, Gladstone, and Queen Victoria's physician. The latter gentleman, Sir Andrew Clark, said that every mouthful of food should be chewed thirty-two times, in order "to give every tooth a chance." McCollum wryly notes that "the teeth work in pairs and that sixteen chews would have accomplished his objective."

Also of great interest are the many instances of scientific breakthroughs antedating the "discoveries" usually described in texts as "firsts." A fine book.

Louis Lasagna

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THE FAMILY HANDBOOK OF HOME NURSING AND MEDICAL CARE. By I. J. Rossman, M.D., and Doris R. Schwartz, R.N. New York, 1958, Random House. Pp. 403, indexed. Price $4.95.

The title of this book clearly describes its purpose, and the two authors have made the contents practical and easily followed by people without training or experience in nursing. Throughout the book, which is long, there is a feeling of warmth and understanding of the needs and problems of both the patient and the family. It stresses the relationship of the family doctor as friend and counselor and the need for close cooperation and mutual understanding among patient, family, and doctor at all times.

The book is divided into seven parts, each part clearly marked in the Table of Contents to provide the means for quick reference to the area of interest.

Part I deals with general information about the responsibilities of families when there is sickness in the home, their attitudes, and preparation to cope with a major illness. It discusses the advantages and disadvantages of hospital, nursing home, or home care and shows how families can review their problems and needs and where they can turn for help.

Part II covers the planning necessary when a sick person is to be cared for at home, the role of the doctor, and the use of the visiting nurse to teach the home nurse how to carry out the doctor's orders for nursing care and treatment. There is discussion of the nutritional needs as well as the occupational and diversional needs of the patient and an excellent chapter on "Understanding Chronic Illness."

Part III discusses the sick child and includes a chapter on "Preparing Your Child for the Hospital" which should help a young mother when the problem arises.

Parts IV and V briefly cover definite chronic diseases, such as cardiovascular disease, cancer, diabetes, tuberculosis, arthritis, and mental illness. There is concrete and up-to-date information that will help the family to understand the patient and his illness. The seriousness of the diseases is clearly stated but in a manner that should alert the family to the dangers without unduly frightening them. The chapter on "Getting Over a Stroke" is particularly well done and full of practical information.

Part VI stresses the need to avoid panic. It gives some brief first-aid directions and cites some common emergencies while stressing the need for accident prevention.

Part VII describes the practical side of taking care of a patient in bed and has many good line drawings to illustrate the procedure necessary to carry out the various types of treatment ordered by the doctor.

Throughout, the book stresses the need to plan and develop routines. There is some repetition of information, probably necessary because of the format. While written for the home nurse it is an excellent reference book for those taking nurses' aid and home nursing courses and would be very valuable to public health nurses. The depth and warmth of feeling so evident throughout the book together with its practical information make it worthwhile reading for anyone caring for the sick.

Ethel Turner

MEN, MOLDS, AND HISTORY. By Félix Martí-Ibáñéz. New York, 1958, MD Publications, Inc. Pp. 114. Price $3.00.

This little book is a compilation of ten essays by Dr. Martí-Ibáñéz, Professor of the History of Medicine at New York Medical College, Editor-in-Chief of *MD Medical Newsmagazine*, and Associate Editor of *Antibiotics and Chemotherapy* and *Antibiotic Medicine and Clinical Therapy*. The author attempts to evaluate the influence of antibiotics on clinical medicine, the medical literature, medical teaching, and research—in short, he tries to show how these drugs have changed the medical world physiologically, psychologically, and philosophically. The book is an out-and-out eulogy of antibiotics and Dr. Martí-Ibáñéz does not hesitate to point out that medicine of the preantibiotic era is an anachronism, which has fallen by the wayside with the advent of the "antibiotic crusade." As long as the discussion remains within the realm of history, art, or philosophy the author, obviously a man of great culture and knowledge, remains the master of his subject. However, when he discusses the beneficial impact of antibiotics on clinical medicine, he illustrates his argument with a series of pseudoscientific statements which do not withstand critical analysis. For example, antibiotics are given credit as effective prophylactic agents following surgery or in situations in which respiratory infections are a hazard, when there is ample evidence that the drugs have not prevented infections under these circumstances; antimicrobial resistance is dismissed lightly as a natural consequence of the discovery of new chemotherapeutic drugs despite the well-known fact that infections with resistant organisms are frequently more serious than those originally treated with antibiotics; oxytetracycline is described as fulfilling a dream in chemotherapy in the face of much evidence that resistant staphylococcal infections are a frequent by-product of the use of this agent; and, the empiric success achieved with antibiotics in the absence of accurate diagnostic data is cited as providing valuable knowledge for the physician of the future. In his enthusiasm, the author speaks of "antibiotic science" and "antibiotic medicine" as generic disciplines, when it seems obvious that all of the scientific data dealing with these agents can be categorized into one of the recognized basic and clinical sciences. Similarly there is little justification for some of the author's other pet projects such as "Professorships of Antibiotic Medicine," and "International Institute of Antibiotics," a "Museum of Antibiotics," etc. The statement describing the pharmaceutical industry as the "scientific subconscious" responsible for the majority of significant discoveries in antibiotic research, completely ignores the fact that the industry's motives are far from altruistic. Finally, the author's claim that "an important source of scientific information for the physician today, a source worthy of a place alongside textbooks and medical journals, is the scientific literature prepared and sent to physicians by pharmaceutical companies" is a flagrant exaggeration, particularly when viewed in the light of a recent exposé of drug house advertising. (See the *Saturday Review of Literature*, December, 1958.)

It is not the purpose of this reviewer to belittle the great contributions to clinical therapy made by antibiotics. Certainly many lives have been and will continue to be saved with these agents. On the other hand, their prolific use has brought with it many problems including hypersensitivity reactions, antimicrobial resistance, and worst of all, the attitude of "treat first and

diagnose later" on the part of many physicians. What seems to be needed is not a document praising antibiotics to the skies, but a critical, dispassionate judgment of the role of these drugs and the problems attendant on their use. This book does not fulfill such a need.

Robert G. Petersdorf

CENTAUR. ESSAYS ON THE HISTORY OF MEDICAL IDEAS. By Félix Martí-Ibáñez, M.D. New York, 1958, MD Publications, Inc. Pp. 715, indexed. Price $6.00.

The author of this fat "new" book is an extraordinary phenomenon. Spanish-born, but a resident of the United States for the past 20 years, he is probably the most successful medical journalist in the country. His showiest enterprise is the throwaway *MD Medical Newsmagazine* (which many physicians apparently do not throw away). The magazine is printed in *Time* format, and serves up a moderately entertaining mixture of medical news, drug house earning reports, medical history, sex, and psychiatry.

Centaur, however, is an irritating and dull scissors-and-paste collection of material previously published (for the most part) in Martí-Ibáñez's own journals. There are numerous names and facts (some of them wrong: ". . . the mechanism by which insulin liberates hexokinase from the anterior hypophysis is known . . .") but little in the way of unifying thought. The prose is at times purplish, at times pedantic, almost always extremely mortal. The longer pieces are so disjointed as to seem dictated on the fly, in bits, on different days, and then never subjected to blue-pencilling. Some of the psychoanalytic stuff is appalling:

"Even chess moves have a profound psychoanalytic meaning. Some players constantly protect their Queen-Mother in order to attain greater power over the King-Father. To crown Pawns and to exchange them for Queens is to reinforce the attack against the King, by converting Pawns—weak little men—(psychoanalytically interpreted as castrated) into strong Amazon-like women with a tremendous sex and war drive."

Topping off the performance is a collection, at the end, of what must be close to every editorial ever written for *MD Medical Newsmagazine*. It seems incredible that the author should have had the gall to consider these pieces deserving of republication, and even more amazing that he felt it necessary to include three editorials documenting the success of his magazine!

The life and personality of Martí-Ibáñez, written by a perceptive, critical journalist, would probably make fascinating reading. His own writings, however, are a dreary business.

Louis Lasagna

UNDERSTANDING APHASIA, A Guide for Family and Friends. By Martha L. Taylor, M.A. Patient Publication No. 2—1958, The Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center. Pp. 48. Price 50¢. (Institute of Physical Medicine and Rehabilitation, 400 East 34th Street, New York 16, New York.)

This is an attractive, well-written, 50-page booklet which should indeed prove to be a very useful guide for the family and friends of patients with aphasia. It is organized around 40 common questions about aphasia which are listed in a Table of Contents. The short answers to these questions given in nontechnical language make up the body of the booklet. A useful check list of "Do's and Don'ts" for dealing with aphasia patients and a 7-page description of services available through the Office of Vocational Rehabilitation and The National Society for Crippled Children and Adults are also included.

The general subjects covered by the questions include the causes of aphasia, the functional significance of the various specific disabilities, common concomitant mental and physical symptoms, and management, therapy, and prognosis of the condition. Language training is described as the only direct treatment, and perhaps the gravest shortcoming in the book is the failure to spell out clearly that even with the best treatment many patients fail to make progress. The author's therapeutic enthusiasm (based on "experience" rather than scientific evidence) may serve the desirable goal of encouraging families to bring in patients for early treatment. It may,

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however, give the misleading impression that onset time or type of therapy is the most important factor in improvement. As a result, in the many cases where biologic limitation to improvement is the critical factor, failure to improve may be regarded as personal failure related to the adequacy of language training.

The great emphasis Mrs. Taylor places throughout the booklet on treating the patient as an "intelligent adult" and "not as a child" is well deserved. Again her therapeutic enthusiasm makes her underemphasize the severe lowering of mental abilities with aphasia. It would perhaps have been less misleading to suggest treating the patient as a "mentally handicapped, though in many ways intelligent adult." Dr. Rusk correctly points out in his introduction to the booklet that "aphasia has been one of the least understood and most poorly managed medical problems both diagnostically and therapeutically." It is to the great credit of this booklet that, in providing simple answers for lay readers to the complex questions about aphasia, so little violence has been done to the facts.

Henry J. Mark

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FUN FOR THE NOT-SO-YOUNG. By Sid G. Hedges. New York, 1958, Philosophical Library, Inc. Pp. 142. Price $3.75.

Mr. Hedges is somewhat of an expert on leisure time interests and recreational activities. He has written many books on "things to do" for young people which have been well received. His interest in the "not-so-young" is rather recent, but equally as welcome and definitely needed.

This little book is a handy guide for a happier and more useful life especially geared to the individual over 50, retired or not—bedridden or up and around. *Fun for the Not-So-Young* is just this—a guide. There are no pat formulas for dealing with specific problems, for it is merely meant to stimulate interests. Follow-through is left to the reader.

There are three main sections, headed "Fun for One," "Fun for Two or Three," and "Fun Together." In the first section, Mr. Hedges describes the joys of being alone and suggests many ways of exploring the self and nature. Home museums, trips, scrapbooks, hobbies, and crafts are among the amusements suggested. New attitudes toward old pastimes are introduced and the probing of new areas of interest is encouraged, for example, learning a new language.

The section entitled "Fun for Two or Three" is more or less a continuation of the first section adding the fun of sharing experiences with someone else. An interesting new approach to the old tradition of visiting the sick was introduced in this section. It was directed toward the patient, suggesting that the patient plan to make the visit as pleasant as possible for the guests and giving plenty of ideas for doing so.

"Fun Together," the third and last section, gives many ideas for conducting meetings in clubs and organizations. How to organize a club is not mentioned, but one would assume that the reader would be motivated to seek out established clubs or find a way to start his own.

This book is an excellent reference book for the social worker, public health nurse, or any other member of a profession where problems of the aged are involved. There are few among us today who could not profit from reading this book and having it around for use now or later on.

Alma J. McKeldin

THE PRINCIPLES AND PRACTICE OF MEDICINE. A Textbook for Students and Doctors. By Sir Stanley Davidson. Ed. 4, Baltimore, 1958, The Williams & Wilkins Co. Pp. 1,067, indexed. Price $8.00.

The fourth edition of this popular textbook follows the same pattern as its predecessors. In just over 1,000 pages is condensed a wealth of basic information. The anatomic and physiologic introduction to each section is an outstanding feature.

One often hears general textbooks of this type criticized on the grounds that they supply a mass of facts without stimulating the reader to further thought, and in places the text does appear to be dogmatic. However the criticism can be answered in several ways. First, the student commencing his clinical years needs facts before he can formulate ideas. Second, the common diseases are discussed in a broad manner with frequent comments on recent developments. Finally, al-

though the more advanced student and postgraduate student may not find sufficient detail to satisfy him, at the end of each chapter further sources of information are recommended.

In conclusion, the editor and his colleagues are to be congratulated once more on producing a book which provides an excellent introduction to clinical medicine and a sound source of reference for all the diseases most commonly encountered.

Keith A. Manley

TUBERCULOSIS: PREVENTION AND CONTROL. By H. W. Hetherington, M.D., M.R.C.P. (London), and Fannie W. Eshleman, R.N., B.S. New York, 1958, G. P. Putnam's Sons. Pp. 404, indexed. Price $6.50.

This textbook is primarily designed for public health nurses, but it is well worth study by anyone interested in the current methods of prevention and control of tuberculosis, one of the most ancient and famous of chronic diseases. The indications and necessary arrangements for family study, for follow-up, and for BCG, and the methods of control are excellently described. About one-tenth of the book is devoted to diagnosis, about half to treatment, and the remainder to the public health and nursing aspects. The chapter on tuberculosis case finding describes the current methods including x-ray surveys in adult populations and repeated tuberculin testing in school children. The authors do not enter the contested field of the dangers of repeated photofluorograms in young adults, but in other respects their discussion of the control of tuberculosis in nurses is one of the best sections in the book. They describe in detail the public health nurse's role in the long-term management of the patient and his family and give sufficient of the pathologic and clinical background of the disease for her to remain intellectually interested in the long process of recovery and the sometimes frustrating task of tracking contacts. The value of conferring with other agencies interested in the family and the importance of coordination, persistence, and constant encouragement are stressed repeatedly. There is a slight tendency throughout, a tendency perhaps unavoidable in textbooks written from the public health and preventive point of view, to present the patient as a somewhat tiresome or recalcitrant person, not always psychologically well adjusted, surrounded by well-meaning and expert helpers whose advice he often unwisely ignores. Despite this, the discussion, for instance, of tuberculous alcoholics is warm and sympathetic and there is no doubt that the authors' skill is accompanied by the devotion and understanding so essential in treating chronic disease of whatever nature. The discussion of treatment is full and expert. Despite the natural reluctance to give an authoritative pronouncement on prognosis in general terms, one felt that some inkling might be given the reader of the *average* time required for clearing, for example, of a new active lesion without cavitation in a cooperative patient on antimicrobial therapy and would help the nurse explain better to her patient the advantages of therapy.

While reading part of this book, I was listening to *La Bohème* on the radio and felt that this opera, *La Dame aux Camélias*, and *The Magic Mountain* should be added to the excellent list of references. The authors quote Moorman as saying "There is nothing so discouraging to domestic infelicity, especially when accompanied by an incapacitating disease and the haunting fear of inconstancy." If the word dramatic were substituted for discouraging, how many novelists and playwrights would agree. Among the agencies and the committees, the home visits and the syringes, the nurse should remember, as the authors have done, the drama and the pathos of the individual patient.

L. M. Haroutunian